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

17-AUG-2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **PP#s 9F05096; 9F06007; 8F04973; 9E06003; and ID# 00ND0025.** Glyphosate in/on Alfalfa Hay and Forage; Field Corn Forage; Stover and Straw of the Cereal Grains Crop Group; Numerous Minor Crops; and Flax in North Dakota. **HED Risk Assessment.**

DP Barcode: D267588
PRAT Case #: 291967
Submission #: S562250

CAS #: 1071-83-6
Chemical #: 417300
Class: Herbicide

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Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509C)

THROUGH: G. Jeffrey Herndon, Acting Branch Senior Scientist
RAB1/HED (7509C)

TO: Robert Forrest/Hoyt Jamerson, PM Team 43
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Registration Division (RD) (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational/residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed new uses of glyphosate in addition to all existing glyphosate uses.

A summary of the findings and an assessment of human risk resulting from the proposed and registered uses of glyphosate is provided in this document. The risk assessment, residue chemistry data review, and dietary exposure risk assessment were provided by William Donovan of RAB1, the hazard assessment by William Dykstra of RAB1, the occupational/residential

review by Myrta Christian of RAB1, and the water exposure assessment by Pat Jennings of the Environmental Fate & Effects Division (EFED).

Recommendation for Tolerances/Registration

Provided that Monsanto submits a revised Section B for glyphosate use on corn indicating a 30-day plant-back interval and revised Section F indicating proposed tolerances of 0.1 ppm for "egg"and "poultry, meat", and 1.0 ppm for "poultry, meat byproducts", the residue chemistry and toxicological databases support the establishment of permanent tolerances for residues of glyphosate [N-(phosphonomethyl)glycine] in/on the following commodities at the recommended tolerance levels indicated in Table 1:

Table 1. Listing of Recommended Glyphosate Tolerance Levels for Raw Agricultural Commodities (RACs).

RAC	Recommended Tolerance (ppm)	RAC	Recommended Tolerance (ppm)
Alfalfa, forage	175	Lesquerella, seed	0.1
Alfalfa, hay	400	Leucaena, forage	200
Aloe vera	0.5	Ligonberry	0.2
Ambarella	0.2	Mamey apple	0.2
Artichoke, globe	0.2	Meadowfoam, seed	0.1
Bamboo, shoots	0.2	Mioga, flower	0.2
Berry group	0.2	Mustard, seed	0.1
Biriba	0.2	Nut, pine	1.0
Betelnut	1.0	Okra	0.5
Blimbe	0.2	Oregano, Mexican, leaves	2.0
Borage, seed	0.1	Palm heart, leaves	0.2
Cactus, fruit	0.5	Papaya, mountain	0.2
Cactus, pads	0.5	Pawpaw	0.2
Chaya	1.0	Pepper leaf, fresh leaves	0.2
Corn, field, forage	3.0	Perilla, tops	1.8
Crambe, seed	0.1	Poultry, meat byproducts* Poultry, meat	1.0 0.1
Custard apple	0.2	Pulasan	0.2

Dokudami	2.0	Quinoa, grain	5.0
Egg	0.1	Rapeseed, meal	15
Epazpote	1.3	Rapeseed, seed	10
Feijoa	0.2	Rose apple	0.2
Flax, meal	8.0	Safflower, seed	0.1
Flax, seed	4.0	Salal	0.2
Galangal, roots	0.2	Sesame, seed	0.1
Ginger, white, flower	0.2	Spanish lime	0.2
Gourd, buffalo, seed	0.1	Spices subgroup	7.0
Governor's Plum	0.2	Star apple	0.2
Gow Kee, leaves	0.2	Stevia, dried leaves	1.0
Grain, cereal, stover and straw, group	100	Surinam cherry	0.2
Herbs subgroup	2.0	Teff, grain	5.0
Hop, dried cones	7.0	Ti, leaves	0.2
Ilama	0.2	Ti, roots	0.2
Imbe	0.2	Ugli fruit	0.5
Imbu	0.2	Wasabi, roots	0.2
Jojoba, seed	0.1	Water spinach, tops	0.2
Juneberry	0.2	Watercress, upland	0.2
Kava, roots	0.2	Wax jambu	0.2
Kenaf, forage	200	Yacon, tuber	0.2

* The existing tolerances for "poultry kidney" and "poultry liver" should be removed when the "poultry, meat byproducts" tolerance is established.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

Monsanto Company has submitted petitions to increase the permanent tolerance levels for residues of the herbicide glyphosate, N-(phosphonomethyl)glycine, in or on the raw agricultural commodities alfalfa hay and forage, and field corn forage; and to establish a new tolerance on stover and straw of the cereal grains crop group. In addition, the Interregional Project No. 4 (IR-4) has submitted a petition to establish permanent tolerances for glyphosate residues in/on numerous minor crops.

Permanent tolerances are established under 40 CFR §180.364 (a)(1) for the combined residues of glyphosate, N-(phosphonomethyl)glycine, and its metabolite aminomethylphosphonic acid (AMPA) resulting from the application of the isopropylamine salt of glyphosate and/or the monoammonium salt of glyphosate in or on numerous commodities; under §180.364 (a)(2) for residues of glyphosate in or on the commodities durian, mangosteen, and rambutan at 0.2 ppm; and under §180.364 (a)(3) for residues of glyphosate resulting from the application of the isopropylamine salt of glyphosate and/or the monoammonium salt of glyphosate in or on several commodities. Under 40 CFR §180.364 (d), tolerances are established for indirect or inadvertent residues of glyphosate and AMPA resulting from their use of irrigation water containing residues of 0.5 ppm following applications on or around aquatic sites, at 0.1 ppm on several crop groups. Where tolerances are established at higher levels from other uses of glyphosate in or on the subject crops, the higher tolerance applies.

Glyphosate is a member of the phosphono amino acid class of chemicals. These compounds are foliar-applied herbicides that interfere with normal plant amino acid synthesis, resulting in the inhibition of nucleic acid metabolism and protein synthesis. Glyphosate blocks the activity of an enzyme, 5-enolpyruvylshikimate 3-phosphate synthase (EPSP synthase), that is involved in aromatic amino acid biosynthesis and that is produced only by green plants. Consequently, glyphosate is toxic to all green plants and essentially nontoxic to other living organisms (G.W. Ware, The Pesticide Book, 1994).

However, the following regulatory history of this chemical is of interest. In 1985, the carcinogenic potential of glyphosate was first considered by a panel (then called the Toxicology Branch Ad Hoc Committee) comprised of members of the Toxicology Branch of the Hazard Evaluation Division. The Committee, in a consensus review dated 04-MAR-1985, classified glyphosate as a Group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The Committee also concluded that dose levels tested in a 26-month rat feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in this species.

The kidney slides from the long-term mouse feeding study were subsequently reexamined by several pathologists, and one pathologist diagnosed an additional kidney tumor in control males. These findings were presented to the FIFRA Scientific Advisory Panel (SAP) which proposed

that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP, in their meeting of 11/12-FEB-1986 (report dated 24-FEB-1986), concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings. A new 2-year rat study was performed up to the limit dose of 20,000 ppm.

The HED Carcinogenicity Peer Review Committee (CPRC) convened on 26-JUN-1991 to discuss and evaluate the weight of the evidence on glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that glyphosate should be classified as a Group E chemical (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species.

As part of their consideration, the CPRC examined data on the following tumors observed in the second rat study: pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. None of them were considered to be biologically significant. As for the mouse study, the CPRC concluded that the renal tubular neoplasms in high dose male mice were not compound-related due to the lack of pairwise significance and the lack of pre-neoplastic kidney lesions in males.

Dose Response Assessment

On March 26, 1998, the HED Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database, selected doses and endpoints for chronic dietary risk assessment, considered the carcinogenic potential and addressed the sensitivity of infants and children from exposure to glyphosate as required by the Food Quality Protection Act (FQPA) of 1996 (HED Doc. No. 012586, W. Dykstra and J. Rowland, 20-APR-1998).

The FQPA Safety Factor Committee (SFC) met on April 6, 1998 and addressed the potential enhanced sensitivity to infants and children as required by FQPA (HED Doc. 012584, B. Tarplee and J. Rowland, 17-APR-1998). The Committee recommended the 10X FQPA Safety Factor be reduced to 1X in assessing the risk posed by this chemical because: 1) the toxicology data base is complete; 2) there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to glyphosate (in the prenatal developmental toxicity study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of appreciable maternal toxicity), and 3) the use of generally high quality data, conservative models and/or assumptions in the exposure assessment provides adequate protection of infants and children.

An acute dose and endpoint were **not** selected for any population subgroups because no effects that could be attributed to a single exposure (dose) were observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits. Therefore, a dose and endpoint were not identified for acute dietary risk assessment.

The chronic reference dose (cRfD) of 2.0 mg/kg/day was based on a rabbit developmental toxicity study. The no-observed-adverse-effect level (NOAEL) of 175 mg/kg/day was based on death, diarrhea, and nasal discharge in female rabbits at the lowest-observed-adverse-effect level (LOAEL) of 350 mg/kg/day. The NOAEL for maternal toxicity in the rabbit developmental toxicity study was the lowest NOAEL of all the major studies which include the 24-month mouse carcinogenicity study [NOAEL = 750 mg/kg/day], the 1-year dog study [NOAEL = 500 mg/kg/day], 2-year chronic/onco rat study [NOAEL = 400 mg/kg/day], 2-generation rat reproduction study [NOAEL = 500 mg/kg/day] and rat developmental toxicity study [NOAEL = 1000 mg/kg/day]. An uncertainty factor (UF) of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variation (10X). The chronic population adjusted dose (cPAD) is a modification of the cRfD to accommodate the FQPA Safety Factor. The cPAD is equal to the cRfD divided by the FQPA Safety Factor. Because the 10X safety factor was reduced to 1X, **the cPAD is equivalent to the cRfD of 2.0 mg/kg/day.**

Based on the lack of evidence of carcinogenicity in mice and rats at doses that were judged to be adequate to assess the carcinogenic potential, glyphosate was classified as a **"Group E"** chemical.

No short-, intermediate-, or long-term dermal endpoints were selected due to the lack of dermal or systemic toxicity following repeated dermal applications of technical glyphosate at 0, 100, 1000 or 5000 mg/kg/day, 6 hours/day, 5 days/week for three consecutive weeks to male and female New Zealand White rabbits. Similarly, inhalation risk assessments (any time period) are not required based on the low toxicity of the formulation products (Toxicity Category III or IV) and the physical characteristics of the technical product (wetcake). None of these risk assessments are required since no toxicological endpoints were identified.

Occupational Exposure and Risk Assessment

An occupational exposure assessment was not required since no endpoints of concern for short-, intermediate-, or long-term exposure were identified.

Dietary Risk Estimates (Food Only)

The chronic dietary exposure analysis for glyphosate was performed using the Dietary Exposure Evaluation Model (DEEM™ version 7.075). Tolerance level residues, default concentration factors, and 100% crop treated (CT) assumptions were used (Tier 1 analysis). HED's level of concern for chronic dietary exposure is >100% cPAD. The chronic dietary risk estimates are below HED's level of concern for the general U.S. population and all subgroups (including infants and children). The highest dietary risk estimate was 3.2% cPAD for the Children (1-6

years old) subgroup. **The results of the analysis indicate that the chronic dietary risk estimates associated with the existing and recommended uses of glyphosate do not exceed HED's level of concern for the general U.S. population or any population subgroup (including infants and children).**

Acute doses and endpoints were not selected for the general U.S. population (including infants and children) or the females 13 - 50 years old population subgroup for glyphosate; therefore, an acute dietary exposure analysis was **not** performed. The HIARC classified glyphosate as a **"Group E"** chemical, evidence of non-carcinogenicity to humans by all routes of exposure was based upon studies in mice and rats; therefore, a cancer dietary exposure analysis was **not** performed.

Water

EFED provided a drinking water assessment of glyphosate for direct application to water and for application to crops. For crop applications, the acute and chronic estimated environmental concentration (EEC) for ground water is 0.0038 ppb (from Tier I SCI-GROW modeling). The acute (peak) and chronic (56-day average, including 3X adjustment factor) EECs for surface water (from Tier I GENEEC modeling) are 21 ppb and 0.83 ppb, respectively. The EEC resulting from the registered use of direct glyphosate application to surface water is 230 ppb.

Aggregate Risk Estimates

Aggregate exposure risk assessment was limited to chronic exposure (food + water). Acute, cancer, and short-, intermediate-, and long-term aggregate exposure risk assessments were not performed because an acute dietary endpoint was not selected, glyphosate is not carcinogenic, and no short-, intermediate-, or long-term dermal endpoints were selected, respectively.

Chronic aggregate risk estimates are below HED's level of concern. A Tier 1 chronic dietary exposure analysis for glyphosate was performed using tolerance level residues and assuming 100% CT for all registered and proposed commodities. The chronic analysis applied to the U.S. population and all population subgroups. The chronic dietary exposure estimates (food only) for the general U.S. population and all population subgroups were <4% of the cPAD. Thus, the chronic dietary risk associated with the proposed and registered uses of glyphosate does not exceed HED's level of concern (>100% cPAD). The surface and ground water EECs were used to compare against back-calculated drinking water levels of comparison (DWLOCs) for aggregate risk assessments. For the chronic scenario, the DWLOCs are 69,000 ppb for the U.S. population and 19,000 ppb for children (1 - 6 years old). The ground and surface water EECs for glyphosate are less than HED's DWLOCs for glyphosate in drinking water as a contribution to chronic aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of glyphosate in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time.

Recommendation for Tolerances/Registration

Provided that Monsanto submits a revised Section B for glyphosate use on corn indicating a 30-day plant-back interval and revised Section F indicating proposed tolerances of 0.1 ppm for "egg"and "poultry, meat", and 1.0 ppm for "poultry, meat byproducts", the residue chemistry and toxicological databases support the establishment of permanent tolerances for residues of glyphosate [N-(phosphonomethyl)glycine] in/on the following commodities at the recommended tolerance levels indicated in Table 1:

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Artichoke, globe	0.2	Meadowfoam, seed	0.1
Bamboo, shoots	0.2	Mioga, flower	0.2
Berry group	0.2	Mustard, seed	0.1
Biriba	0.2	Nut, pine	1.0
Betelnut	1.0	Okra	0.5
Blimbe	0.2	Oregano, Mexican, leaves	2.0
Borage, seed	0.1	Palm heart, leaves	0.2
Cactus, fruit	0.5	Papaya, mountain	0.2
Cactus, pads	0.5	Pawpaw	0.2
Chaya	1.0	Pepper leaf, fresh leaves	0.2
Corn, field, forage	3.0	Perilla, tops	1.8
Crambe, seed	0.1	Poultry, meat byproducts* Poultry, meat	1.0 0.1
Custard apple	0.2	Pulasan	0.2
Dokudami	2.0	Quinoa, grain	5.0
Egg	0.1	Rapeseed, meal	15
Epazpote	1.3	Rapeseed, seed	10

Feijoa	0.2	Rose apple	0.2
Flax, meal	8.0	Safflower, seed	0.1
Flax. seed	4.0	Salal	0.2
Galangal, roots	0.2	Sesame, seed	0.1
Ginger, white, flower	0.2	Spanish lime	0.2
Gourd, buffalo, seed	0.1	Spices subgroup	7.0
Governor's Plum	0.2	Star apple	0.2
Gow Kee, leaves	0.2	Stevia, dried leaves	1.0
Grain, cereal, stover and straw, group	100	Surinam cherry	0.2
Herbs subgroup	2.0	Teff, grain	5.0
Hop, dried cones	7.0	Ti, leaves	0.2
Ilama	0.2	Ti, roots	0.2
Imbe	0.2	Ugli fruit	0.5
Imbu	0.2	Wasabi, roots	0.2
Jojoba, seed	0.1	Water spinach, tops	0.2
Juneberry	0.2	Watercress, upland	0.2
Kava, roots	0.2	Wax jambu	0.2
Kenaf, forage	200	Yacon, tuber	0.2

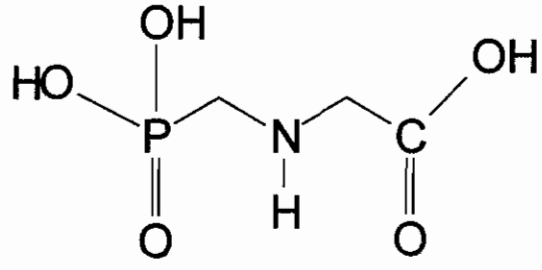
* The existing tolerances for "poultry kidney" and "poultry liver" should be removed when the "poultry, meat byproducts" tolerance is established.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredient

Chemical Name:	N-(phosphonomethyl)glycine
Common Name:	Glyphosate
PC Code Number:	417300
CAS Registry No.:	1071-83-6
Molecular Formula:	$C_3H_8NO_5P$
Molecular Weight:	169.07

2.2 Structural Formula



3.0. HAZARD CHARACTERIZATION

3.1. Hazard Profile

The toxicological data base on glyphosate is complete and will support registration (HED Doc. No. 012586, W. Dykstra and J. Rowland, 20-APR-1998) for existing and proposed uses.

Acute Toxicity

The following table summarizes acute toxicity values and categories for glyphosate:

Table **2.** Acute Toxicity of Glyphosate (Technical)

GDLN	STUDY	RESULTS
870.1100	Acute Oral Toxicity in Rats MRID # 41400603 Acceptable/guideline	LD_{50}: > 4320 mg/kg (both sexes) Effects: Decreased activity and diarrhea TOXICITY CATEGORY: III
870.1200	Acute Dermal Toxicity in Rabbits MRID # 41400603 Acceptable/guideline	LD_{50}: > 2000 mg/kg No deaths or clinical signs TOXICITY CATEGORY: III
870.1300	Acute Inhalation Toxicity in Rats MRID # 41400603 Not Required	The study was waived due to technical being a nonvolatile wetcake (10-15% moisture). Inhalation studies conducted on formulations indicate low degree of toxicity from this route.
870.2400	Primary Eye Irritation in Rabbits MRID # 41400603 Acceptable/guideline	Mild Irritation, clears in 7 days TOXICITY CATEGORY: III

870.2500	Primary Dermal Irritation in Rabbits MRID # 41400604 Acceptable/guideline	Slight irritation TOXICITY CATEGORY: IV
870.2600	Dermal Sensitization in Guinea Pigs MRID # 00137137, 00137138, 00137139, 00137140 Acceptable/guideline	Negative sensitizing reaction

Table 3. Toxicity Profile of Glyphosate.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity in rats	40559401, 00093879 (1987) Acceptable/guideline 0, 1000, 5,000, or 20,000 ppm M & F: 0, 50, 250, or 1,000 mg/kg/day	NOAEL < 50 mg/kg/day for both sexes LOAEL = 50 mg/kg/day based on increased phosphorus and potassium in both sexes
870.3100 90-Day oral toxicity in mice	00036803 (1979) Acceptable/guideline 0, 5,000, 10,000 or 50,000 ppm M & F: 0, 750, 1500, or 7500 mg/kg/day	NOAEL = 1500 mg/kg/day in both sexes LOAEL = 7500 mg/kg/day in both sexes based on decreased body weight gain in both sexes.
870.3200 21/28-Day dermal toxicity in rabbits	00098460 (1982) Acceptable/guideline M & F: 0, 10, 1000 or 5000 mg/kg/day	NOAEL = 1000 mg/kg/day for males and 5000 mg/kg/day for females LOAEL = 5000 mg/kg/day in males based on decreased food consumption
870.3250 90-Day dermal toxicity in rats	NA	NA

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3465 90-Day inhalation toxicity in rats	NA	NA
870.3700a Prenatal developmental toxicity in rats	00046362 (1980) Acceptable/guideline F: 0, 300, 1000, or 3500 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day LOAEL = 3500 mg/kg/day based on mortality, increased clinical signs, and reduced body weight gain **Developmental** NOAEL = 1000 mg/kg/day LOAEL = 3500 mg/kg/day based on decreases in total implantations/dam and nonviable fetuses/dam, increased number of litters and fetuses with unossified sternebrae, and decreased fetal body weight
870.3700b Prenatal developmental toxicity in rabbits	00046363 (1980) Acceptable/guideline F: 0, 75, 175, or 350 mg/kg/day	**Maternal** NOAEL = 175 mg/kg/day LOAEL = 350 mg /kg/day based on mortality, and clinical signs **Developmental** NOAEL = 175 mg/kg/day LOAEL = 350 mg/kg/day (insufficient litters available to assess developmental toxicity)
870.3800 Reproduction and fertility effects in rats	41621501 (1990) Acceptable/guideline 0, 2000, 10,000 or 30,000 ppm F_0F_1 M: 100, 500 or 1500 mg/kg/day, F_0 F_1 F: 100, 500, or 1500 mg/kg/day	**Parental/Systemic** NOAEL = 500 mg/kg/day for males and females LOAEL = 1500 mg/kg/day for males and females based on clinical signs, decreased body weights, decreased weight gain, and decreased food consumption in both sexes **Reproductive/Offspring** NOAEL = 500 mg/kg/day for males and females LOAEL = 1500 mg/kg/day for males and females based on reduced pup weights in both sexes during second and third weeks of lactation

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity in dogs	00153374 (1985) Acceptable/guideline Doses: 0, 20, 100, or 500 mg/kg/day by capsule	NOAEL = 500 mg/kg/day (highest dose tested) LOAEL > 500 mg/kg/day
870.4300 Combined Chronic Toxicity/Carcino-genicity in rats	41643801 (1990) Acceptable/guideline 0, 2000, 8,000 or 20,000 ppm M: 0, 89, 362, or 940 mg/kg/day F: 0, 113, 457, 1,183 mg/kg/day	NOAEL = 362 mg/kg/day in males and 457 mg/kg/day in females LOAEL = 940 mg/kg/day in males and 1,183 mg/kg/day in females based on decreased weight gain in females, and increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased relative liver weight/brain weight in males **(no) evidence of carcinogenicity**
870.4200b Carcinogenicity in mice	00130406, 00150564 (1983) Acceptable/guideline 0, 1000, 5,000 or 30,000 ppm M & F: 0, 150, 750, or 4,500 mg/kg/day	NOAEL = 750 mg/kg/day in males and females LOAEL = 4,500 mg/kg/day in both sexes based on decreased body weight gains in both sexes, increased incidence of renal proximal tubule epithelial basophilia and hypertrophy in females and increased incidence of interstitial nephritis, hepatocellular hypertrophy and hepatocellular necrosis in males **(no) evidence of carcinogenicity**

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5100 in vitro rec-assay with B. subtilis H17 (rec+) and M45 (rec-) and reverse mutation assay using E. coli WP2 hcr and S. typhimurium strains	000132683 (1978) Acceptable/guideline	no evidence of genotoxicity up to the limit dose or cytotoxicity in the presence or absence of metabolic activation
870.5265 in vitro reverse gene mutation assay in S. typhimurium bacteria	00078620 (1978) Acceptable/guideline	no evidence of induced mutant colonies over background in *Salmonella* strains TA 98, TA 100, TA 1535, and TA 1537 both in the presence and absence of metabolic activation at doses up to cytoxic levels or the limit dose
870.5300 in vitro gene mutation assay in Chinese hamster ovary cells/HGPRT	00132681 (1983)	no evidence of genotoxicity up to cytotoxic levels in the presence and absence of metabolic activation
870.5385, bone marrow chromosome aberrations assay	00132683 (1983) Acceptable/guideline	There was no significant increase in the frequency of chromosome aberrations in bone marrow at the limit dose of 1,000 mg/kg in both sexes of Sprague-Dawley rats.
870.6200a Acute neurotoxicity screening battery in rats	NA	NA
870.6200b Subchronic neurotoxicity screening battery in rats	NA	NA

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6300 Developmental neurotoxicity in rats	NA	NA
870.7485 Metabolism in rats	40767101, 40767102 (1988) Acceptable/guideline	Following a single oral dose, 30-36% was absorbed and less than 0.27% was eliminated as CO_2. Urine and feces contained 97.5% as parent. Aminomethylphosphonic acid (AMPA) was only metabolite found at 0.2-0.3% of administered dose. Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in the bone.
870.7600 Dermal penetration	NA	NA

Subchronic Toxicity

In a 90-day feeding study in Sprague-Dawley rats at dietary levels of 0, 1000, 5000, or 20,000 ppm [50, 250, and 1000 mg/kg/day] of glyphosate technical, the NOAEL for systemic toxicity was considered less than 1000 ppm due to increased serum phosphorus and potassium at all treated doses in both sexes and the occurrence of high dose pancreatic lesions in males (pancreas not examined for low and mid-dose groups). This study was designed to be a dose range-finding study for the chronic toxicity study in rats and was not repeated (MRID No. 40559401, 00093879).

In a 90-day feeding study in CD-1 mice, dietary levels of 750, 1500, or 7500 mg/kg/day [5000, 10,000, or 50,000 ppm] of technical glyphosate resulted in a systemic NOAEL of 1500 mg/kg/day with the high dose LOAEL based on decreased weight gains of 24% and 18% in males and females, respectively [MRID No. 00036803].

In a 21-day dermal toxicity study in New Zealand White rabbits, glyphosate was applied to 10/sex/dose [5 with intact and 5 with abraded skin] at levels of 0, 10, 1000, or 5000 mg/kg/day. The rabbits were exposed for 6 hours/day, 5 days/week, for 3 weeks. The systemic NOAEL was 1000 mg/kg/day and the LOAEL was 5000 mg/kg/day, based on decreased food consumption in males. Although serum lactate dehydrogenase was decreased in both sexes at the high dose, this finding was not considered to be toxicologically significant [MRID No. 00098460].

The required 90-day feeding study in dogs is satisfied by the one-year dog feeding study [MRID No. 00153374].

Chronic Toxicity

A chronic feeding/carcinogenicity feeding study in Sprague-Dawley rats was conducted for 26 months at dietary levels of 0, 30, 100, or 300 ppm [0, 3, 10, or 31 mg/kg/day]. There were no systemic effects in any of the parameters examined [body weight, food consumption, clinical signs, mortality, clinical pathology, organ weights and histopathology]. The systemic NOAEL was established at >31 mg/kg/day [MRID No. 00093879].

A second chronic toxicity/carcinogenicity study in Sprague-Dawley rats was conducted at dietary levels of 0, 2000, 8000, or 20,000 ppm [0, 89, 362, or 940 mg/kg/day for males and 0, 113, 457, or 1183 mg/kg/day for females] for 24 months. The systemic NOAEL was established at 8,000 ppm and the LOAEL was identified at 20,000 ppm based on decreased weight gains in the females and increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight and increased relative liver weight/brain weight in males [MRID No. 41643801].

In a one-year chronic toxicity study in beagle dogs, glyphosate technical was administered by gelatin capsule at levels of 0, 20, 100, or 500 mg/kg/day. There were no systemic effects in all examined parameters and the systemic NOAEL was established at > 500 mg/kg/day [MRID No. 00153374].

Carcinogenicity

A chronic feeding/carcinogenicity study in Sprague-Dawley rats was performed at doses of 0, 30, 100, or 300 ppm [0, 3, 10, or 31 mg/kg/day for males and 0, 3, 14, or 34 mg/kg/day for females] for 26 months. At the high-dose, in comparison to concurrent controls, the following results were observed: increased incidence of C-cell thyroid carcinomas in females and an increased incidence of interstitial cell [Leydig cell] testicular tumors. The thyroid tumors were not statistically significant by pairwise comparison to controls and the testicular tumors were within the range of historical controls for studies of comparable duration. It was concluded that the study results were negative for carcinogenicity, but that the dose levels were not high enough to assess carcinogenic potential [00093879].

A chronic feeding/carcinogenicity study was conducted in Sprague-Dawley rats for 24 months at dose levels of 0, 2000, 8000, or 20,000 ppm [0, 89, 362, or 940 mg/kg/day for males and 0, 113, 457, or 1183 mg/kg/day in females]. The results showed increased incidence of pancreatic islet cell adenomas at the low and high dose in males, hepatocellular adenomas at the low and high dose in males, and C-cell thyroid adenomas in both sexes at the mid and high dose group. Each of the tumor types was not considered treatment-related for the following reasons: (1) the pancreatic islet cell tumors had no statistically significant dose-related trend, there was no progression to carcinomas, and the incidence of pancreatic hyperplasia was not dose-related; (2)

the hepatocellular adenomas were within the range of historical controls, these liver tumors were not statistically significant by pairwise comparison to concurrent controls, there was no progression to carcinoma, and the incidence of hyperplasia was not considered compound-related; and (3) the c-cell thyroid tumors were not statistically significant by pairwise comparison and positive dose-related trend, there was no progression to carcinoma, and there was no statistically significant dose-related increase in either incidence or severity of hyperplasia in either sex [MRID No. 41643801].

A carcinogenicity study in CD-1 mice was conducted for 24 months at doses of 0, 150, 750, or 4500 mg/kg/day [0, 1000, 5000, or 30,000 ppm]. There were no effects at the low and mid-doses. At the high dose, an increased incidence of renal tubular adenomas was seen in males, but not in females [zero incidence for all groups]. In males, the incidence was 1, 0, 1, and 3 out of 50/sex/dose. The occurrence of this rare tumor was not statistically significant by pairwise comparison to concurrent controls, but had a statistically significant dose-related trend. There were no tumors associated non-neoplastic lesions in males, but females had an increased incidence of proximal tubule epithelial basophilia and hypertrophy in the absence of any renal tubular neoplasms. In males, there was an increased incidence of interstitial nephritis, hepatocellular hypertrophy and hepatocellular necrosis. There was also statistically significant decreased weight gain in both sexes. The high dose of 30,000 ppm exceeded the limit dose [7000 ppm] for mice. HED concluded, based on a weight-of the evidence evaluation, that the renal tubular adenomas were not compound-related due to the absence of pairwise statistical significance for males, the absence of related non-neoplastic lesion in males, and the presence of related non-neoplastic lesions in females in the absence of renal tubular adenomas. Additionally, the high dose exceeded the limit dose required for testing in mice [MRID No. 00130406, 00150564].

Developmental Toxicity

In the rat developmental toxicity study, Sprague-Dawley rats were dosed by gavage at doses of 0, 300, 1000, or 3500 mg/kg/day during days 6-15 of gestation. The maternal (systemic) NOAEL was 1000 mg/kg/day. The maternal (systemic) LOAEL of 3500 mg/kg/day was based on the following treatment-related effects: diarrhea, decreased mean body weight gain, breathing rattles, inactivity, red matter around the nose and mouth, and on forelimbs and dorsal head, and death (24% of the group). The developmental (fetal) NOAEL is 1000 mg/kg/day. The developmental (fetal) LOAEL of 3500 mg/kg/day was based on treatment-related developmental effects observed only in the high-dose group of: decreases in total implantations/dam and inviable fetuses/dam, increased number of litters and fetuses with unossified sternebrae, and decreased mean fetal body weights [MRID No. 00046362].

In the rabbit developmental toxicity study, Dutch Belted rabbits were gavaged during gestation days 6 - 27 at doses of 0, 75, 175, or 350 mg/kg/day. The maternal (systemic) NOAEL is 175 mg/kg/day. The maternal (systemic) LOAEL of 350 mg/kg/day was based on treatment-related effects that included: diarrhea, nasal discharge, and death (62.5% of does died by gestation day 21). The developmental (pup) NOAEL is ≥175 mg/kg/day (insufficient litters were available at

350 mg/kg/day to assess developmental toxicity). Developmental toxicity was not observed at any dose [MRID No. 00046363].

Reproductive Toxicity

A three-generation reproduction study was conducted with Sprague-Dawley rats at doses of 0, 3, 10, or 30 mg/kg/day [0, 30, 100 or 300 ppm]. The parental NOAEL was ≥ 30 mg/kg/day (highest dose tested). The reproductive NOAEL was 10 mg/kg/day based on an increased incidence of focal tubular dilation of the kidney (both unilateral and bilateral combined) in the 30 mg/kg/day group [high-dose] male F_{3b} pups [MRID No. 00105995].

Since the focal tubular dilation of the kidneys was not observed at the 1500 mg/kg/day level (HDT) in the 2-generation rat reproduction (see below), but was observed at the 30 mg/kg/day level (HDT) in the 3-generation rat reproduction study, the HED RfD Committee concluded that the latter was a spurious rather than glyphosate-related effect. Therefore, the parental and reproductive (pup) NOAELs are ≥30 mg/kg/day.

A two-generation reproduction study was conducted with Sprague-Dawley rats at doses of 0, 2000, 10,000, or 30,000 ppm [0, 100, 5000, or 1500 mg/kg/day]. Treatment-related effects observed in the high dose group included: soft stools, very frequent, in the F_0 and F_1 males and females, decreased food consumption and body weight gain of the F_0 and F_1 males and females during the growth (premating) period, and decreased body weight gain of the F_{1a}, F_{2a} and F_{2b} male and female pups during the second and third weeks of lactation. Focal tubular dilation of the kidneys, observed in the 3-generation study, was not observed at any dose level in this study. Based on the above findings, the parental and developmental (pup) NOAEL's are 500 mg/kg/day and the parental and developmental (pup) LOAEL's are 1500 mg/kg/day. There were no adverse reproductive effects at any dose level [MRID No. 41621501].

Mutagenicity

A gene mutation assay in an Ames Test was conducted using glyphosate, both with and without metabolic activation. The strains of Salmonella typhimurium used were TA98, TA100, TA1535, and TA1537. No increases in reverse mutations were observed at any concentration [MRID No. 00078620].

A gene mutation assay in mammalian cells was conducted using glyphosate in the Chinese hamster ovary (CHO) cells/hypoxanthine-guanine-phosphoribosyl transferase [HGPRT] assay, with and without metabolic activation. No mutagenic response was observed either with or without metabolic activation up to the limit of cytotoxicity [10 mg/ml; MRID No. 00132681].

A structural chromosomal aberration assay was conducted using a single dose of glyphosate administered intraperitoneally [i.p.] to male and female Sprague-Dawley rats. The dose used was 1 g/kg of body weight and the bone marrow cells were examined for clastogenic [chromosome-damaging] effects. No significant clastogenic effects were observed [MRID No. 00132683].

In a fourth study, glyphosate was tested in two assays: the rec-assay using B. subtilis H17 (rec+) and M45 (rec-); and the reverse mutation assays using E. coli WP2 hcr and Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation. No increases in mutations were observed in either study [MRID No. 00078619].

Metabolism

Two metabolism studies with rats are available. In the first study, single or repeated doses of radiolabeled C14-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of C14-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO_2. Ninety-seven point five percent of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methylphosphonic acid (AMPA) was the only metabolite found in urine (0.2 - 0.3% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg/day did not significantly change the metabolism, distribution or excretion of glyphosate [MRID No. 40767101, 40767102].

In a second study, male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled C14-glyphosate. The dose level used for male and female rats was 1150 mg/kg. Blood samples were collected at 0, 0.25, 0.50, 1, 2, 4, 6, and 10 hours after injection. Femoral bone samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after dosing. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.00445 and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately one hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow and that it is even more rapidly eliminated from plasma [MRID No. 00132685].

Neurotoxicity

Neurotoxicity has not been observed in any of the acute, subchronic, chronic, developmental or reproductive studies performed with glyphosate. Glyphosate lacks a leaving group and, therefore, it would not seem likely to inhibit esterases [the presumptive neurotoxic mechanism of concern for all organophosphates]. Neurotoxicity studies in accordance with the 81-7 and 82-7 guidelines have not been requested for glyphosate.

Other Toxicological Considerations

The HIARC (HED Doc. No. 012586, W. Dykstra and J. Rowland, 20-APR-1998) determined that a developmental neurotoxicity assessment was not required based on the following weight-of-evidence:

Glyphosate does not appear to be a neurotoxic chemical. There was no indication of toxicity to the central or peripheral nervous system in subchronic or chronic toxicity studies. No treatment-related alterations in brain weight or histopathology [non-perfused tissues] were observed following exposure to glyphosate and glyphosate does not inhibit acetylcholinesterase.

No evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic doses up to 3500 mg/kg/day and 350 mg/kg/day, respectively.

Glyphosate has a complete database and no other toxicological concerns have been identified in the evaluated studies.

Developmental and Reproductive Toxicity

The oral rat and rabbit developmental studies and the oral rat reproduction study demonstrated no indication of increased sensitivity of rats or rabbits to *in utero and postnatal* exposure to glyphosate.

In the rat developmental toxicity study, Sprague-Dawley rats were dosed by gavage at doses of 0, 300, 1000, or 3500 mg/kg/day during days 6 - 15 of gestation. The maternal (systemic) NOAEL is 1000 mg/kg/day. The maternal (systemic) LOAEL of 3500 mg/kg/day was based on the following treatment-related effects: diarrhea, decreased mean body weight gain, breathing rattles, inactivity, red matter around the nose and mouth, and on forelimbs and dorsal head, and death (24% of the group). The developmental (fetal) NOAEL is 1000 mg/kg/day. The developmental (fetal) LOAEL of 3500 mg/kg/day was based on treatment-related developmental effects observed only in the high-dose group of: decreases in total implantations/dam and inviable fetuses/dam, increased number of litters and fetuses with unossified sternebrae, and decreased mean fetal body weights [MRID No. 00046362].

In the rabbit developmental toxicity study, Dutch Belted rabbits were gavaged during gestation days 6-27 at doses of 0, 75, 175, or 350 mg/kg/day. The maternal (systemic) NOAEL is 175 mg/kg/day. The maternal (systemic) LOAEL of 350 mg/kg/day was based on treatment-related effects that included: diarrhea, nasal discharge, and death (62.5% of does died by gestation day 21). The developmental (pup) NOAEL is ≥175 mg/kg/day (insufficient litters were available at 350 mg/kg/day to assess developmental toxicity). Developmental toxicity was not observed at any dose [MRID No. 00046363].

A three-generation reproduction study was conducted with Sprague-Dawley rats at doses of 0, 3, 10, or 30 mg/kg/day [0, 30, 100 or 300 ppm]. The parental NOAEL is ≥30 mg/kg/day (highest dose tested). The reproductive NOAEL was 10 mg/kg/day based on an increased incidence of focal tubular dilation of the kidney (both unilateral and bilateral combined) in the 30 mg/kg/day group [high-dose] male F_{3b} pups [MRID No. 00105995].

Since the focal tubular dilation of the kidneys was not observed at the 1500 mg/kg/day level (Highest Dose Tested (HDT)) in the 2-generation rat reproduction (see below), but was observed at the 30 mg/kg/day level (HDT) in the 3-generation rat reproduction study, the HED RfD Committee concluded that the latter was a spurious rather than glyphosate-related effect. Therefore, the parental and reproductive (pup) NOAELs are ≥30 mg/kg/day.

A two-generation reproduction study was conducted with Sprague-Dawley rats at doses of 0, 2000, 10,000, or 30,000 ppm [0, 100, 5000, or 1500 mg/kg/day]. Treatment-related effects observed in the high dose group included: soft stools, very frequent, in the F_0 and F_1 males and females, decreased food consumption and body weight gain of the F_0 and F_1 males and females during the growth (premating) period, and decreased body weight gain of the F_{1a}, F_{2a} and F_{2b} male and female pups during the second and third weeks of lactation. Focal tubular dilation of the kidneys, observed in the 3-generation study, was not observed at any dose level in this study. Based on the above findings, the parental and developmental (pup) NOAEL's are 500 mg/kg/day and the parental and developmental (pup) LOAEL's are 1500 mg/kg/day. There were no adverse reproductive effects at any dose level [MRID No. 41621501].

3.2. FQPA Considerations

The FQPA Safety Factor Committee (SFC) met on April 6, 1998 and addressed the potential enhanced sensitivity to infants and children as required by FQPA (HED Doc. 012584, B. Tarplee and J. Rowland, 17-APR-1998). The Committee recommended the 10X FQPA Safety Factor be reduced to 1X in assessing the risk posed by this chemical because: 1) the toxicology data base is complete; 2) there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to glyphosate (in the prenatal developmental toxicity study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of appreciable parental toxicity), and 3) the use of generally high quality data, conservative models and/or assumptions in the exposure assessment provide adequate protection of infants and children.

3.2.1. Cumulative Risk

EPA does not have, at this time, available data to determine whether glyphosate has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that glyphosate has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether glyphosate shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for glyphosate need to be modified or revoked.

3.2.2. Endocrine Disruption

FQPA (1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of glyphosate and its end-use products for endocrine effects may be required.

3.3. Dose Response Assessment

Acute Dietary Endpoint: An acute dietary endpoint and dose was not identified in the toxicology data base by the HIARC (HED Doc. No. 012586, W. Dykstra and J. Rowland, 20-APR-1998). A review of the rat and rabbit developmental studies did not provide a dose or endpoint that could be used for acute dietary risk purposes. Additionally, there were no data requirements for acute or subchronic rat neurotoxicity studies since there was no evidence of neurotoxicity in any of the toxicology studies at very high doses and glyphosate lacks a leaving group. This risk assessment is not required.

Chronic Dietary Endpoint: Groups of 16/dose Dutch Belted rabbits were dosed with technical glyphosate at doses of 0, 75, 175, or 350 mg/kg/day between gestation days 6 to 27. Maternal effects were seen at only the high dose and consisted of diarrhea, nasal discharge and death [10/16]. Developmental effects were not seen at any dose tested. Therefore, the NOAEL and LOAEL for maternal toxicity were 175 mg/kg/day and 350 mg/kg/day, respectively. The NOAEL for maternal toxicity in the rabbit developmental study was the lowest NOAEL of all the major studies which include the 24-month mouse carcinogenicity study [NOAEL = 750 mg/kg/day], the 1-year dog study [NOAEL = 500 mg/kg/day], 2-year chronic/onco rat study [NOAEL = 400 mg/kg/day], 2-generation rat reproduction study [NOAEL = 500 mg/kg/day] and rat developmental study [NOAEL = 1000 mg/kg/day]

An uncertainty factor (UF) of 100 was applied to account for inter-(10X) and intra-(10X) species variation. The **10X** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **was reduced to 1X, since there was no special sensitivity for infants and children.** For chronic dietary risk assessment, **a UF of 100 is adequate** for protection from exposure to glyphosate because:

(i) Developmental studies showed no increased sensitivity in fetuses as compared to maternal animals following **in utero** exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups as compared to adults.

(iii) The toxicology database is complete and there are no data gaps.

Consequently, the cRfD is 2.0 mg/kg/day. Because the 10X Safety Factor was reduced to 1X, the cPAD is equivalent to the cRfD of 2.0 mg/kg/day.

Cancer Assessment: Glyphosate is classified as Category E: not carcinogenic in two acceptable animal studies.

Dermal Absorption: A dermal absorption factor is not applicable since dermal risk assessments are not required. However, a dermal penetration of 3% was determined in an in vitro human dermal penetration study [MRID No. 00251737].

Short- and Intermediate-Term Occupational and Residential Exposure Risk Assessments: In a 21-day dermal toxicity study with technical glyphosate, the NOAEL was 1000 mg/kg/day and the LOAEL was 5000 mg/kg/day based on decreased food consumption in females [MRID No. 00098460]. Although the rabbit developmental study had a maternal toxicity NOAEL of 175 mg/kg/day, use of the 3% dermal absorption with this oral NOAEL of 175 mg/kg/day yields a dermal NOAEL > 5000 mg/kg/day. This risk assessment is not required.

Chronic Occupational and Residential (Non-Cancer) Exposure Risk Assessments: A dose and endpoint were not identified for this risk assessment. This risk assessment is not required.

Inhalation Exposure (General and Long-Term Considerations) Risk Assessments: Formulations of glyphosate are Toxicity Category III or IV and technical glyphosate is a wetcake. The acute inhalation study was waived for technical glyphosate. A dose and endpoint were not identified for this risk assessment. This risk assessment is not required.

Recommendation for Aggregate Exposure Risk Assessments: An aggregate exposure risk assessment for glyphosate should include contributions from food and water exposures.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 4.

Table 4. Summary of Toxicological Dose and Endpoints for Glyphosate for Use in Human Risk Assessment[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	not applicable	not applicable	There were no effects that could be attributed to a single exposure (dose) in oral toxicity studies including the developmental toxicity studies in rats and rabbits.
Chronic Dietary all populations	NOAEL= 175 mg/kg/day UF = 100 **Chronic RfD** = 2.0 mg/kg/day	FQPA SF = 1 **cPAD** = chronic RfD / FQPA SF = 2.0 mg/kg/day	Rabbit Developmental study: mortality, diarrhea, and nasal discharge at 350 mg/kg/day.
Short-, Intermediate-, and Long-Term Dermal (Occupational/ Residential)	not applicable	not applicable	No systemic toxic effects seen at doses up to 1000 mg/kg/day in the 21 day dermal toxicity study.
Inhalation (any time period) (Occupational/ Residential)	not applicable	not applicable	Based on low toxicity of formulations and technical material [wet cake] inhalation study was waived.
Cancer (oral, dermal, inhalation)	"Group E" chemical	not applicable	There is no evidence of carcinogenic potential. Therefore, a cancer risk assessment is not required.

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose.

4.0. Exposure Assessment

4.1 Summary of Proposed Uses

Alfalfa

Monsanto Company submitted supplemental labeling for preharvest application of Roundup Ultra to alfalfa. Roundup Ultra may be used in declining alfalfa stands or any stand of alfalfa where crop destruction is acceptable. The label allows use of up to 2 quarts of product per acre per year (1.5 lbs acid equivalents (ae)/A/year), but specifies a minimum interval of 36 hours between application and harvest. Application may be made at any time of the year. There is a restriction against use on alfalfa grown for seed.

Field Corn
Monsanto Company submitted supplemental labeling for postemergence applications of Roundup Ultra to corn with the Roundup Ready® gene. Roundup Ultra may be applied to Roundup Ready corn from emergence through the V8 stage (8 leaves with collars) or until corn height reaches 30 inches, whichever comes first.

Maximum yearly rates. Preplant: The maximum amount of this product which can be applied prior to crop emergence is 5 quarts per acre (3.75 lbs ae/A). In crop: Sequential in-crop applications of this product from emergence through the V8 stage or 30 inches must not exceed 2 quarts per acre (1.5 lbs ae/A) per growing season. Preharvest: The maximum amount of this product that can be applied after maximum kernel fill is complete and the crop is physiologically mature (black layer formation) until 7 days before harvest is 1 quart per acre (0.75 lb ae/A). Thus, the combined total per year for all applications may not exceed 8 quarts per acre (6.0 lbs ae/A).

Allow a minimum of 50 days between application of this product and harvest of corn forage and 7 days between application and harvest of corn grain. Allow a minimum of 10 days between in-crop applications of this product. There are no rotational crop restrictions following applications of this product.

This product may be applied by ground (in 5 - 20 gallons of spray solution per acre) or aerial (in 3 - 15 gallons of spray solution per acre) methods.

Cereal Grains Crop Group
Monsanto Company submitted supplemental labeling for preharvest application of Roundup Ultra to barley. Apply up to 1 quart of this product per acre (0.75 lb ae/A) in 5 to 10 gallons of water per acre using aerial or ground spray equipment. Roundup Ultra may be used when grain has 30% grain moisture or less, and at least 7 days prior to harvest. It is not recommended that barley grown for seed be treated because a reduction in germination or vigor may occur. Preharvest applications of this product are not recommended for malting barley.

The proposed label specifies essentially the same use rate and pattern as the Canadian label for Roundup Transorb Herbicide (essentially the same as Roundup Ultra). The Canadian label does not include the recommendation against preharvest treatments in barley intended for malting, and prohibits application to barley grown for seed production. The preharvest use pattern specified for barley is also allowed for the other cereal grain crops.

Minor Crops
Separate use directions are specified for orchard type crops (including crop types with growth habits, culture and harvested portion similar to the labeled crop categories "citrus crops", "small fruits and berries", "tree fruits", "tree nuts", "tropical crops" and "vine crops") and other food crops (including other crop types that have similar growth habits, culture, and harvested portion similar to labeled crop categories "asparagus", "cereal crops", "corn", "grain sorghum (milo)", "peanuts", and "vegetable crops" in addition to other crops such as culinary herbs and

medicinal/nutraceutical plants). For orchard type crops, the instructions allow preplant (site preparation), strips (in row), chemical mowing (growth suppression), and middles (between rows). The directions emphasize that extreme care must be taken to ensure no part of the tree is contacted by herbicide solution, spray drift, or mist. For other food crops, the instructions allow chemical fallow, preplant fallow beds, preplant, preemergence, post-directed hooded, and postharvest applications. Preplant applications must be made at least 3 days prior to transplanting. The preemergence application must be made prior to the emergence of the crop. Post-directed hooded applications are applied to mulched or unmulched row middles after crop establishment and must be made at least 14 days prior to harvest. Postharvest applications may be applied after the final harvest to control weeds or suppress regrowth of annual crops or for renovation of biennial or perennial crops beds, and must be made at least 14 days prior to planting the next crop. Treated vegetation may not be harvested or fed to animals.

Application rates are dependent on the weeds to be controlled, and range from 0.37 to 5 quarts of Roundup Ultra per acre per year (0.28 to 3.75 lbs acid equivalents of glyphosate acid per acre per year).

Flax
Monsanto Company submitted supplemental labeling for preharvest application of Roundup Ultra to flax under Section 18 emergency exemption to expire 01-OCT-2000. Apply up to 1 quart (0.75 lb ae/A) in 3 to 20 gallons of water per acre when the crop is physiologically mature and nearly ready to harvest. Apply when the crop is 30% or less grain moisture. Either ground broadcast or aerial applications may be made. A 2% solution can be used when using hand-held or backpack sprayers.

Allow at least 7 days before harvest. Only one application per year may be made. Employ at least a 30-day plant-back interval between treatment and replanting for any crop not listed in the Roundup Ultra herbicide label.

Conclusion: The proposed uses of glyphosate are adequately described. However, there is a 30-day plant-back interval (PBI) for crops on which the use of glyphosate is not registered. Thus the statement that "There are no rotational crop restrictions following applications of this product", should be replaced with the 30-day PBI restriction on the supplemental label for corn. A revised Section B should submitted.

4.2. Dietary Exposure

4.2.1. Food Exposure

Residue chemistry data pertaining to the proposed uses of glyphosate were submitted and reviewed by HED (D262424, W. Donovan, 18-JAN-2000; D256740, W. Donovan, 09-JUN-2000; D256742, W. Donovan, 23-JUN-2000; D245594, W. Donovan, 29-JUN-2000).

Nature of the Residue - Plants

The qualitative nature of the residue in plants is adequately understood. Studies with a variety of plants including corn, cotton, soybeans, and wheat indicate that the uptake of glyphosate or its metabolite, aminomethylphosphonic acid (AMPA), from soil is limited. The material which is taken up is readily translocated. Foliarly applied glyphosate is readily absorbed and translocated throughout the trees of vines to the fruit of apples, coffee, dwarf citrus (calamondin), pears and grapes. Metabolism via N-methylation yields N-methylated glycines and phosphonic acids. For the most part, the ratio of glyphosate to AMPA is 9 to 1 but can approach 1 to 1 in a few cases (e.g., soybeans and carrots). Much of the residue data for crops reflects a detectable residue of parent (0.05 - 0.15 ppm) along with residues below the level of detection (<0.05 ppm) of AMPA (Memo, R. Perfetti, 27-OCT-1992). In a meeting of the HED Metabolism Committee held 19-AUG-1992, the Committee determined that AMPA need not be regulated and should be dropped from the tolerance expression (Memo, R. Perfetti, 19-OCT-1992). Furthermore, in a meeting of the HED Metabolism Committee held 17-MAR-1994, the Committee discussed whether uses that result in significantly higher residues of AMPA in plants and livestock commodities in the future would require that AMPA be reintroduced into the tolerance expression of glyphosate. The Committee determined that, based on toxicological considerations, AMPA need not be regulated regardless of levels observed in foods or feeds (Memo, R. Perfetti, 17-MAR-1994). Thus, the terminal residue to be regulated in plants is glyphosate *per se*.

Nature of the Residue - Livestock

The qualitative nature of the residue in livestock is adequately understood. Studies with lactating goats and laying hens fed a mixture of glyphosate and AMPA indicate that the primary route of elimination was by excretion (urine and feces). These results are consistent with metabolism studies in rats, rabbits, and cows. The terminal residues in eggs, milk, and animal tissues are glyphosate and its metabolite AMPA; there was no evidence of further metabolism (Memo, R. Perfetti, 27-OCT-1992). The conclusions of the HED Metabolism Committee on 19-AUG-1992 and 17-MAR-1994 apply to plant and livestock commodities. Thus, the terminal residue to be regulated in livestock is glyphosate *per se*.

Residue Analytical Methods

Adequate enforcement methods are available for analysis of residues of glyphosate in or on plant and livestock commodities. These methods include GLC (Method I in *Pesticides Analytical Manual (PAM) II*; the limit of detection is 0.05 ppm) and HPLC with fluorometric detection. Use of the GLC method is discouraged due to the lengthiness of the experimental procedure. The HPLC procedure has undergone successful Agency validation and was recommended for inclusion in PAM II (Memo, R. Perfetti, 27-OCT-1992). A GC/MS method for glyphosate in crops has also been validated by EPA's Analytical Chemistry Laboratory (ACL) (PP#5F04555, G. Kramer, 21-MAR-1995).

Adequate analytical methods are available for residue data collection and enforcement of the proposed tolerances of glyphosate in or on alfalfa forage and hay, field corn forage, stover and straw of the cereal grains crop group, livestock commodities, and the minor crops listed in Tables 5 and 6.

Multiresidue Methods
The Pestrak database (1990) indicate that recoveries are not likely for glyphosate under FDA Multiresidue Methods. No further data regarding multiresidue methods are required for this proposed use.

Storage Stability Data
The available storage stability data indicate that residues of glyphosate are stable under frozen storage conditions (-20°C): in or on plant commodities for a period of 1 year, in animal commodities for 2 years, and in water for 1 year (Memo, R. Perfetti, 27-OCT-1992). No additional storage stability data are needed.

Crop Field Trials

Alfalfa Hay & Forage
Monsanto Company submitted crop field trial data supporting the proposed use rate in MRID 430770-01, which was previously reviewed and found acceptable by HED (D201255, M.I. Rodriguez, 12-JAN-1995). To summarize, glyphosate residues in alfalfa forage treated at a rate of 1.5 lbs ae/A (equivalent to 2 quarts of Roundup Ultra per acre) with a 1-day PHI ranged from 48 - 158 ppm. Glyphosate residues in alfalfa hay treated at a rate of 1.5 lbs ae/A (equivalent to 2 quarts of Roundup Ultra per acre) with a 3-6 day PHI (to allow for drying) ranged from 44 - 377 ppm. **The available crop field trial data support tolerances of 175 and 400 ppm for alfalfa forage and hay, respectively.**

Field Corn Forage
Previously submitted residue data (MRID 437127-02) were generated with a proprietary line of Roundup Ready Corn, identified as line 599-04-2, genetically modified to express proteins that confer tolerance to glyphosate. This line expresses both CP4 5-enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS) and glyphosate oxidoreductase (gox). The CP4 EPSPS enzyme confers tolerance through a modified target-site for glyphosate action. The gox enzyme provides a second mechanism of tolerance by converting glyphosate to AMPA.

Monsanto has developed a second-generation of Roundup Ready Corn which has been transformed to express a modified version of the wild-type EPSPS enzyme found in corn. This line, identified as GA21, does not express the gox enzyme. Without the gox degradation gene, the primary residue is parent glyphosate. This change in the biochemical processing of glyphosate by the corn plant has led to the need for additional corn field trials to ensure adequate tolerance glyphosate levels in corn RACs.

Monsanto Company submitted crop field trial data from 22 corn residue field trials conducted during 1997 in AL, GA, IA (3), IL (3), IN, KS (2), MI (2), MN, NE, OH, OK, PA, SD, and WI (3). Extensive hurricane damage at a AL site resulted in dropping the site from the study prior to collection of any samples. No grain or stover sample were collected at the OH site due to loss of

crop from animal feeding. These data were previously reviewed and found acceptable by HED (D245594, W. Donovan, 29-JUN-2000).

The number and geographical distribution of corn field trials is adequate. **The available crop field trial data depicting glyphosate residues in the GA21 line of Roundup Ready Corn support the existing tolerances of 1.0 and 100 ppm for corn grain and stover, and support a new tolerance of 3.0 ppm for corn forage.**

Stover and Straw of Cereal Grains Crop Group

Monsanto Company submitted barley field trial data supporting the proposed use rate in MRID 438072-02, which were previously reviewed and found acceptable by HED (D221254, T. Bloem, 24-AUG-1998). To summarize, following treatment with Roundup® Herbicide at rates ranging from 0.60 to 1.6 lb ae/A with 10 - 21 day pre-harvest intervals (PHIs), glyphosate residues in barley straw ranged from 0.7 - 21.6 ppm in the Canadian field trials. These crop field trial data support a tolerance level of 25 ppm for barley, straw. However, the petitioner requests a crop group tolerance of 100 ppm based on the following existing tolerance levels for the representative crops of crop group 16:

corn, field, stover	100 ppm
sorghum, grain, stover	40 ppm
wheat, straw	85 ppm

Because the range of appropriate tolerances for the representative crops is less than 5-fold, and the same use pattern (preharvest) applies to all the crops in this group, a crop group tolerance is appropriate.

Existing glyphosate tolerances on "corn, field, stover", "sorghum, grain, stover", and "wheat, straw" together with the available barley crop field trial data from Canada support a crop group tolerance of 100 ppm for "grain, cereal, stover and straw, group".

Miscellaneous Minor Crops

In a 12-JAN-2000 meeting of the Chemistry Science Advisory Council, approval of the following tolerances for minor crops requested by the IR-4 program was granted, with the caveat that the approach described here is acceptable FOR GLYPHOSATE ONLY, and is based on the low toxicity of glyphosate, the extensive existing glyphosate database, the plant-growth regulating action of glyphosate, and the relatively low consumption of the minor crops specified.

Herbs subgroup

IR-4 proposes that EPA establish a 2.0 ppm glyphosate tolerance for the herbs subgroup based on the established 0.2 ppm tolerance on leafy vegetables (except Brassica) group (Crop Group 4) divided by the percent dry matter (%DM) for fresh basil (10%). The dry down factors utilized for basil and all the commodities as needed in this memo were taken from Dr. Bernie Schneider's memo to W. Donovan entitled "Glyphosate IR-4 Chemistry Draft Dry Down Factors", 22-OCT-

1999. **HED recommends establishment of a herbs subgroup tolerance of 2.0 ppm derived by translating the existing glyphosate tolerance from crop group 4 (leafy vegetables (except Brassica)) using the fresh basil percent dry matter as a correction factor to account for drying.**

Spices subgroup

IR-4 proposes that EPA establish a 7.0 ppm glyphosate tolerance for the spices subgroup based on translation of the established 7.0 ppm tolerance for instant tea. **Based on the lack of toxicity concerns and the similarity of use patterns, HED recommends establishment of a spices subgroup tolerance of 7.0 ppm derived by translating the existing glyphosate tolerance from instant tea to the spices subgroup.**

Other Miscellaneous Minor Crops

IR-4 also proposes that EPA establish the proposed glyphosate tolerances listed in Tables 5 and 6 for miscellaneous crops, based on data translations for similar crops. Table 5 shows calculation of proposed tolerances making use of the existing leafy vegetable tolerance together with a correction factor for percent dry matter (%DM), while Table 6 includes those crops whose drying (if any) is accounted for by the translation crop.

Table 5. Proposed glyphosate tolerances for commodities whose drying (if any) is not accounted for by the translation crop.

RAC	%DM	Translation crop(s)	Translation crop tolerance (ppm)	Proposed Tolerance[1] (ppm)
chaya	20	leafy vegetables	0.2	1.0
dokudami	10	leafy vegetables	0.2	2.0
epazote	16	leafy vegetables	0.2	1.3
oregano, mexican, leaves	10	leafy vegetables	0.2	2.0
perilla, tops	11	leafy vegetables	0.2	1.8

[1] Calculated as [Translation tolerance]/[%DM].

Table 6. Proposed tolerance levels for crops whose drying (if any) is accounted for by the translation crop.

RAC	Translation crop(s)	Translation crop tolerance (ppm)	Proposed tolerance (ppm)
ambarella	guava	0.2	0.2

RAC	Translation crop(s)	Translation crop tolerance (ppm)	Proposed tolerance (ppm)
blimbe	guava	0.2	0.2
imbu	guava	0.2	0.2
rose apple	guava	0.2	0.2
surinam cherry	guava	0.2	0.2
biriba	sugar apple	0.2	0.2
ilama	sugar apple	0.2	0.2
imbe	sugar apple	0.2	0.2
pawpaw	sugar apple	0.2	0.2
governor's plum	papaya	0.2	0.2
mamey apple	papaya	0.2	0.2
papaya, mountain	papaya	0.2	0.2
aloe vera	cucurbit vegetables	0.5	0.5
cactus, fruit	cucurbit vegetables	0.5	0.5
cactus, pads	cucurbit vegetables	0.5	0.5
nut, pine	tree nuts	1.0	1.0
betelnut	tree nuts	1.0	1.0
pistachio*	tree nuts	1.0	1.0
stevia, dried leaves	dried tea	1.0	1.0
ugli fruit	citrus fruits	0.5	0.5
crambe, seed	sunflower seed	0.1	0.1
mustard, seed	sunflower seed	0.1	0.1
rapeseed, seed	sunflower seed	0.1	0.1
safflower, seed	sunflower seed	0.1	0.1
borage, seed	sunflower seed	0.1	0.1
gourd, buffalo, seed	sunflower seed	0.1	0.1

RAC	Translation crop(s)	Translation crop tolerance (ppm)	Proposed tolerance (ppm)
jojoba, seed	sunflower seed	0.1	0.1
lesquerella, seed	sunflower seed	0.1	0.1
meadowfoam, seed	sunflower seed	0.1	0.1
sesame, seed	sunflower seed	0.1	0.1
artichoke, globe	brassica (cole) leafy vegetables	0.2	0.2
bamboo, shoots	brassica (cole) leafy vegetables	0.2	0.2
palm heart, leaves	brassica (cole) leafy vegetables	0.2	0.2
kava, roots	carrot, potato, radish	0.2	0.2
galangal, roots	carrot, potato, radish	0.2	0.2
ginger, white, flower	leafy vegetable	0.2	0.2
wasabi, roots	carrot, potato, radish	0.2	0.2
yacon, tuber	carrot, potato, radish	0.2	0.2
gow kee, leaves	leafy vegetables	0.2	0.2
mioga, flower	leafy vegetables	0.2	0.2
pepper leaf, fresh leaves	leafy vegetables	0.2	0.2
ti, leaves	leafy vegetables	0.2	0.2
ti, roots	leafy vegetables	0.2	0.2
water spinach, tops	leafy vegetables	0.2	0.2
watercress, upland	leafy vegetables	0.2	0.2
hops cones, dried	instant tea	7.0	7.0
juneberry	berry group	0.2	0.2
lingonberry	berry group	0.2	0.2

RAC	Translation crop(s)	Translation crop tolerance (ppm)	Proposed tolerance (ppm)
salal	berry group	0.2	0.2
kenaf, forage	nongrass animal feed group	200	200
leucaena, forage	nongrass animal feed group	200	200
okra	cucurbit vegetables	0.5	0.5
quinoa, grain	wheat grain	5.0	5.0
teff, grain	wheat grain	5.0	5.0

* Pistachio already has a tolerance of 0.2 ppm for glyphosate residues. The current proposal to increase this level to 1.0 ppm is intended to harmonize the pistachio tolerance with that of the tree nut crop group.

Based on the lack of toxicity concerns and the similarity of use patterns, HED recommends for establishment of the tolerances listed in Tables 5 and 6.

Flax

In support of a Section 18 emergency exemption from the state of North Dakota (ID # 00ND0025), the Interregional Research Project No. 4 (IR-4) submitted the results of seven flax field trials conducted in North Dakota and South Dakota. The maximum glyphosate residue in these field trials was 3.5 ppm; thus, the appropriate glyphosate tolerance level for "flax, seed" is 4.0 ppm. IR-4 indicated that additional flax field trials are in progress. Once these results are available, the flax tolerance levels will be adjusted as necessary.

Processed Food

Flax

In support of a Section 18 emergency exemption from the state of North Dakota (ID # 00ND0025), IR-4 submitted the results of one flax processing study. Glyphosate residues in flax meal and oil were 7.1 and <0.05 ppm, respectively, when processed from flax seed with a residue level of 3.5 ppm. Based on this study, the glyphosate flax meal concentration factor is 2.0. The product of the concentration factor and the highest average field trial (HAFT) for flax seed gives a glyphosate level of 7.1 ppm in flax meal. Thus, the appropriate tolerance level for "flax, meal" is 8.0 ppm, while no tolerance is needed for "flax, oil".

Meat, Milk, Poultry, and Eggs

Because of the many potential feed items for which glyphosate tolerances are established, glyphosate reviews have made use of more realistic livestock diets to estimate dietary burdens (D201255, M.I. Rodriguez, 12-JAN-1995; and D238398, J. Garbus and T. Morton, 18-SEP-1998). Most recently, dietary burdens of 210 and 220 ppm were estimated for dairy and beef cattle, respectively; and of 65 and 74 ppm for swine and poultry, respectively (D256740, W.

Donovan, 09-JUN-2000). The cattle dietary burdens included a contribution from alfalfa hay as the roughage component of the diet, with a tolerance of 400 ppm. Comparison of the dietary burdens to available residue levels from cattle, hog and hen feeding studies demonstrated that existing glyphosate tolerance levels for all livestock liver and kidney (except poultry) are adequate, but that tolerance levels of 0.05 and 1.0 ppm are needed for egg and poultry meat byproducts, respectively. **However, in order to harmonize with CODEX, HED now recommends a tolerance level of 0.1 ppm for "egg", and a level of 0.1 ppm for "poultry, meat" in addition to a level of 1.0 ppm for "poultry, meat byproducts". A revised Section F including these tolerance levels is needed.**

Rotational Crops
There is a 30-day minimum plant-back interval for crops on which the use of glyphosate is not registered (Memo, G. Kramer, 12-MAY-1994).

International Harmonization of Tolerances
Several maximum residue limits (MRLs) for glyphosate have been established by CODEX in or on various commodities (see Attachment 1). Based on toxicological considerations, HED has determined that AMPA no longer needs to be regulated regardless of levels observed in foods or feeds and should be deleted from the tolerance expression (Memo, R. Perfetti, 17-MAR-1994). Thus, harmonization with the MRLs for AMPA is not possible. The existing and recommended "rape, seed" tolerance of 10 ppm is already in harmony with the CODEX MRL. The recommended "corn, forage" tolerance of 3.0 ppm is based on crop field trial data obtained when using a new strain of Roundup Ready corn and thus cannot be lowered to achieve harmonization with the CODEX MRL of 1.0 ppm for "maize, forage". There is no conflict between the CODEX MRL of 0.1 ppm for "poultry, meat" and the recommended U.S. tolerance of 1.0 ppm for "poultry, meat byproducts" as these commodities are not the same. Finally, although the available data support a tolerance of 0.05 ppm for egg, for harmonization purposes and because no risk issues are involved, a tolerance level of 0.1 ppm for "egg" is recommended.

4.2.2. Dietary Exposure Analysis

HED conducts dietary risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. A chronic dietary exposure and risk analysis (food only) was conducted in order to provide an estimate of the dietary exposure and associated risk for glyphosate resulting from existing and recommended tolerance levels (D265038, W. Donovan, 31-JUL-2000). For chronic dietary risk assessments, residue estimates for foods or food-forms of interest are multiplied by the 3-day averaged consumption estimate of each food for each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

Acute Dietary Exposure Analysis
An acute dietary endpoint and dose was not identified by the HIARC (26-MAR-1998). Therefore, an acute dietary exposure analysis was not performed.

Chronic Dietary Exposure Analysis

A conservative analysis was conducted using published and recommended tolerance level residues, 100% CT assumptions, and default concentration factors for all commodities. The cPAD used for all population subgroups was 2.0 mg/kg/day. For chronic dietary risk estimates, HED's level of concern is for exposures >100% cPAD. Dietary exposure estimates for the U.S. Population and other representative subgroups are presented in Table 7. Due to the conservative assumptions employed, the results in Table 7 represent an overestimate of the chronic human dietary exposure.

Many of the minor crops listed in Tables 5 and 6 are not included in the current version of the DEEM™ program because of their low consumption levels. In conducting this chronic dietary risk assessment, HED has made the reasonable assumption that exclusion of these minor crops would not significantly change the results listed in Table 7 below. Evidence for the validity of this assumption comes from the DEEM™ analysis conducted in support of the present actions (D267589, W. Donovan, 31-JUL-2000), which made use of glyphosate tolerance levels prior to consideration of harmonization with CODEX MRLs (i.e., egg at 0.05 ppm and no poultry, meat tolerance). A test run conducted 10-AUG-2000 with egg and poultry meat both included at 0.1 ppm produced no differences from the 31-JUL-2000 analysis when expressing %cPAD using two significant figures.

Table 7. Summary of Results from Chronic DEEM™ Analysis of Glyphosate.

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.0301	1.5
All infants (< 1 year old)	0.0617	3.1
Children (1-6 years old)	0.0647	3.2
Children (7-12 years old)	0.0432	2.2
Females 13-50 years old	0.0224	1.1
Males 13-19 years old	0.0303	1.5
Seniors 55+ years old	0.0218	1.1

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years old). Thus, the population subgroups listed in Table 7 include those subgroups having sufficient numbers of survey respondents in the CSFII food consumption survey to be considered statistically reliable.

Cancer Dietary Exposure Analysis

The carcinogenic potential of glyphosate has been evaluated by the HED Cancer Peer Review Committee (26-MAR-1998) and classified as a Group E chemical--no evidence of carcinogenicity in two acceptable animal species. Thus, a cancer risk assessment is not required.

4.2.3. Drinking Water Exposure

HED followed the "Interim Guidance for Incorporating Drinking Water Exposure into Aggregate Risk Assessments", issued on 01-AUG-1999 (SOP 99.5). Thus, the GENEEC and SCI-GROW models were run by the EFED to produce estimates of glyphosate concentrations in surface and ground water, respectively. The primary use of these models is to provide a coarse screen for sorting out pesticides for which there is a high degree of confidence that the true levels of the pesticide in drinking water will be less than the human health drinking water levels of concern (DWLOCs). A human health DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that chemical from food, water, and residential sources, if applicable.

Only limited monitoring data are available for glyphosate at this time; and these data are not suitable for use in a quantitative drinking water risk assessment. Specifically, a level of 150 ppb was detected in a Texas well. The presence of this level was attributed to substandard well construction and careless use of chemicals. Six samples from wells in Virginia had detectable residues of glyphosate ranging from 0.004 to 0.009 ppb. Consequently, the EFED provided a Tier 1 drinking water assessment for glyphosate (D264647 and D264649, Pat Jennings, xx-AUG-2000). This assessment utilized the GENEEC and SCI-GROW screening models to provide estimates of ground and surface water contamination resulting from glyphosate treatment of crops at the maximum label rate. However, as glyphosate may be applied directly to water, EFED separately assumed application at the maximum label rate of 3.75 lb ae/A to a body of water six feet deep to estimate possible surface water concentrations of glyphosate. Limitations and assumptions for these screening models are documented in EFED memoranda. The following information about environmental fate, and ground and surface water EECs was taken directly from the applicable EFED memoranda (D264647 and D264649, Pat Jennings, xx-AUG-2000; Memo, Kevin Poff and Ibrahim Saheb, 15-MAY-1998).

Environmental Fate Assessment

The available field and laboratory data indicate that glyphosate adsorbs strongly to soil and would not be expected to move vertically below the 6 inch soil layer. Based on unaged batch equilibrium studies glyphosate and glyphosate residues are expected to be immobile with Kd(ads) values ranging from 62 to 175. The mechanism of adsorption is unclear; however, it is speculated that it may be associated with vacant phosphate sorption sites or high levels of metallic soil cations. The data indicate that chemical and photochemical decomposition is not a significant pathway of degradation of glyphosate in soil and water. However, glyphosate is readily degraded by soil microbes to AMPA, which is degraded to CO_2, although at a slower rate than parent glyphosate.

Based on the low vapor pressure of glyphosate, volatilization from soils will not be an important dissipation mechanism. The low octanol/water partition coefficient suggests that glyphosate will have a low tendency to accumulate in fish.

Ground Water EECs

Using available fate parameters and assuming two applications with a retreatment interval of 90 days at a rate of 5 lbs ai/A (3.75 lbs ae/A), the ground water EEC from glyphosate using SCI-GROW was 0.0038 ppb. The current label allows multiple applications of 0.37 - 5 lbs ai/A up to a maximum of 10.6 lbs ai/A/year. There may be circumstances under which ground water concentration could exceed the SCI-GROW estimates. However, such exceptions should be rare since the SCI-GROW model is based exclusively on maximum ground water concentrations from studies conducted at sites and under conditions which are most likely to result in ground water contamination. The groundwater EECs generated by SCI-GROW are based on the largest 90-day averaged recorded during the sampling period. Since there is relatively little temporal variation in groundwater concentrations compared to surface water, the concentrations can be considered as acute and chronic values [D264647 and D264649, Pat Jennings, xx-AUG-2000].

Surface Water EECs

The GENEEC model was used to estimate surface water concentrations for glyphosate resulting from its maximum use rate on crops. GENEEC is a single event model (one runoff event), but can account for spray drift from multiple applications. GENEEC represents a 10 hectare field immediately adjacent to a 1 hectare pond that is 2 meters deep with no outlet. The pond receives a spray drift event from each application plus one runoff event. The runoff event moves a maximum of 10% of the applied pesticide into the pond. This amount can be reduced due to degradation on the field and by soil sorption. Spray drift is estimated at 5% of the application rate. The GENEEC values represent upper-bound estimates of the concentrations that might be found in surface water due to glyphosate use. Thus, the GENEEC model predicts that glyphosate surface water EECs range from a peak of 21 ppb to a 56-day average of 2.5 ppb [D264647 and D264649, Pat Jennings, xx-AUG-2000]. For comparison purposes, HED guidance suggests dividing the 56-day GENEEC EEC value by 3 before comparison to the calculated $DWLOC_{chronic}$ value ["Interim Guidance for Incorporating Drinking Water Exposure into Aggregate Risk Assessments", 01-AUG-1999 (SOP 99.5)]. Thus, 2.5 ÷ 3 or 0.83 ppb is the predicted surface water EEC value resulting from glyphosate treatment of crops.

To estimate the possible concentration of glyphosate in surface water resulting from direct application to water, EFED assumed application to a water body six feet deep [D264647 and D264649, Pat Jennings, xx-AUG-2000]. At an application rate of 3.75 lb ae/A, the estimated concentration is 230 ppb. Because the glyphosate water-application estimate is greater than the crop-application estimate, 230 ppb is the appropriate value to compare to the calculated $DWLOC_{chronic}$ value for aggregate risk considerations.

DWLOCs

HED has calculated DWLOCs for chronic exposure to glyphosate in surface and ground water. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the sum of

the chronic dietary food exposure (from DEEM™) and the chronic residential exposure estimate was subtracted from the cPAD to obtain the chronic water exposure in drinking water. DWLOCs were then calculated using the default body weights and drinking water consumption figures listed in Table 8.

Table 8. Default Body Weight and Drinking Water Consumption Figures.

DEEM ™ Population	Body Weights (kg)	Drinking Water Consumption (liters/day)
General U.S. Population/48 States	70	2
Females 13-50 years old	60	2
Infants/children	10	1

The chronic DWLOC values were calculated using the following equation:

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times (\text{body weight (kg)})]}{[\text{consumption (L/day)} \times 10^{-3}\ \text{mg}/\mu\text{g}]}$$

where chronic water exposure (mg/kg/day) = [cPAD - (average food + residential exposure) (mg/kg/day)], and residential exposure is taken to be zero.

The chronic DWLOCs for the U.S. Population, females 13-50 years old, and children (1-6 years) population subgroups are 69,000, 59,000, and 19,000 ppb, respectively.

4.3. Occupational and Residential Exposure and Risk Assessment/Characterization

Summary of Use Patterns and Formulations

Glyphosate is a non-selective herbicide registered for numerous food and non-food crops and a variety of other uses including ornamentals, greenhouses, residential areas, lawns, and industrial rights of way. Glyphosate is formulated in liquid and solid forms and it is applied using ground or aerial equipment.

Occupational and Residential Handler Exposures

Based on the registered uses of glyphosate, the potential for occupational and residential exposures exists. However, based on the low acute toxicity and the lack of other toxicological concerns, glyphosate does not meet HED's criteria for occupational and residential data requirements.

Occupational and Residential Post-Application Exposures
The HIARC (HED Doc. No. 012586, W. Dykstra and J. Rowland, 20-APR-1998) determined that short-, intermediate-, and long-term dermal or inhalation risks assessments are not required since toxicological concerns were not identified via these routes of exposures. Exposures from occupational and/or residential uses of glyphosate are not expected to pose undue risks.

Restricted Entry Interval (REI)
The REI established by the Worker Protection Standard (WPS) for Agricultural Pesticides for glyphosate is 12 hours. This REI is based on glyphosate acute toxicity classification by the dermal and ocular routes of exposures. Glyphosate is in Toxicity Category III for both routes of exposure.

Incident Reports
Glyphosate has been the subject of numerous incident reports, primarily for eye and skin irritation injuries, in California. Some glyphosate end-use products are in Toxicity Categories I and II for eye and dermal irritation. The Reregistration Eligibility Decision Document for Glyphosate (SEP-1993) indicates the Agency is not adding additional personal protective equipment (PPE) requirements to labels of end-use products, but that it continues to recommend the PPE and precautionary statements required for end-use products in Toxicity Categories I and II.

5.0. Aggregate Exposure and Risk Assessment Characterization

Aggregate exposure risk assessment was limited to chronic exposure (food + water). Acute, cancer, and short-, intermediate-, and long-term aggregate exposure risk assessments were not performed because an acute dietary endpoint was not selected, glyphosate is not carcinogenic, and no short-, intermediate-, or long-term dermal endpoints were selected, respectively.

5.1. Acute Aggregate Risk

There was no acute dietary endpoint identified, therefore a risk assessment was not conducted.

5.2. Short- and Intermediate-term Aggregate Exposure and Risk

Short-term and intermediate-term dermal and inhalation risk assessments for occupational and residential exposures are not required due to the lack of significant toxicological effects observed.

5.3. Chronic Aggregate Exposure and Risk

Chronic aggregate risk assessments are below HED's level of concern. Using conservative exposure assumptions (tolerance-level residues, default concentration factors, and 100% CT), HED has calculated that the maximum percentage of the cPAD that will be utilized by dietary (food) exposure to residues of glyphosate is 3.2 % percent for children (1-6 years old). Despite

the potential for exposure to glyphosate in drinking water, HED does not expect the aggregate exposure to exceed 100% of the cPAD. HED bases this determination on a comparison of glyphosate EECs in surface and ground water to calculated DWLOCs. The glyphosate EECs in surface and ground water are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with the pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, HED will reassess the potential impact of glyphosate in food and drinking water as part of the aggregate chronic risk assessment process.

Table 9 summarizes the quantitative aspects of the aggregate risk assessment for chronic exposure to glyphosate. For chronic exposure to glyphosate in surface and ground water, the DWLOCs are 69,000 μg/L for U.S. Population and 19,000 μg/L for children (1 - 6 years old). The glyphosate EECs in surface and ground water are 230 and 0.004 ppb, respectively. These values are less than HED's level of comparison for glyphosate in drinking water as a contribution to chronic aggregate exposure. **Therefore, taking into account present uses and uses proposed in this action, HED concludes that there is a reasonable certainty that no harm will result to any population subgroup from chronic aggregate exposure to glyphosate residues.**

Table 9. Aggregate Risk Assessment for Chronic Exposure to Glyphosate.

Population Subgroup	cPAD mg/kg/day	Dietary Exposure mg/kg/day	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Chronic DWLOC (ppb)
General U.S. Population	2.0	0.0301	230	0.004	69000
All Infants (<1 year old)	2.0	0.0617	230	0.004	19000
Children (1-6 years old)	2.0	0.0647	230	0.004	19000
Children (7-12 years old)	2.0	0.0432	230	0.004	20000
Females (13-50 years old)	2.0	0.0224	230	0.004	59000
Males (13-19 years old)	2.0	0.0303	230	0.004	69000
Males (20+ years old)	2.0	0.0256	230	0.004	69000
Seniors (55+ years old)	2.0	0.0218	230	0.004	69000

6.0. DEFICIENCIES / DATA NEEDS

6.1. Toxicology

★ None

6.2. Chemistry

★ Revised supplemental labeling for field corn use specifying a PBI of 30-days for non-labeled crops.

★ Revised Section F specifying proposed tolerances of 0.1 ppm for "egg", 0.1 ppm for "poultry, meat", and 1.0 ppm for "poultry, meat byproducts".

6.3. Occupational/Residential Exposure

★ None

7.0. ATTACHMENTS

Attachment 1: International Residue Limit (Codex) Status Sheet.

cc with attachment: W. Donovan, W. Dykstra, M. Christian
RDI: RAB1 Team 2 (8/16/00); Branch (8/16/00);RAB1 Chemists (8/2/00)
W. Donovan:806R:CM2:(703)305-7330:7509C:RAB1

Attachment 1

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: N-(phosphonomethyl)glycine	Common Name: glyphosate	X□ Proposed tolerance □ Reevaluated tolerance □ Other	Date: 8/2/00

Codex Status (Maximum Residue Limits)	**U. S. Tolerances**
□ No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Numbers: 9F05096, 9F06007, 8F04973, 9E06003, and 00ND0025. DP Barcode: D267588
Residue definition (step 8/CXL): glyphosate. Separate tolerances proposed for AMPA for maize, at step 6.	Reviewer/Branch: W. Donovan/RAB1
	Residue definition: glyphosate per se

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
Maize forage	1	See Table 1	
Maize forage (step 6)	2 AMPA		
Egg	0.1 (*)		
poultry, meat	0.1 (*)		
rape seed	10		
maize fodder (step 6)	5 AMPA		

Limits for Canada	**Limits for Mexico**
□ No Limits □ No Limits for the crops requested	□ No Limits □ No Limits for the crops requested
Residue definition: N-(phosphonomethyl)glycine, including the metabolite amino-methylphosphonic acid	Residue definition: glifosato

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
kidney of cattle, goats, hogs, **poultry** and sheep	2	alfalfa	200
liver of cattle, goats, hogs, **poultry** and sheep	0.2	Mustard	0.2

Notes/Special Instructions: Codex has MRLs for some cereal grains: barley 20; oats 20; sorghum 20; rice 0.1 (*); corn grain 1 (2 AMPA proposed at step 6); wheat 5; but NO MRLs for stover and straw of any of these.
Canada has MRLs for several cereals, but NOT specifically for stover and straw: barley, 10; oats, 10; wheat, 5; corn, 3.
Mexico has MRLs for several cereals, but NOT specifically for stover and straw: corn, 1; rice, 0.1; oats, 20; barley, 20; sorghum, 15; wheat, 5. S. Funk, 08/03/2000.

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Chemical:	**Glyphosate (ANSI)**
PC Code:	**417300**
HED File Code	**14000 Risk Reviews**
Memo Date:	**08/17/2000**
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