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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 20-FEB-2002

SUBJECT: PP#s 0F06130, 0F06195, and 0F06273. **GLYPHOSATE IN/ON PASTURE AND RANGELAND GRASSES, ROUNDUP READY® WHEAT, AND NONGRASS ANIMAL FEEDS. Health Effects Division (HED) Risk Assessment.**
Barcode D280831. PC Codes 103601 & 417300. Case 292955. Submission S579658.

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THROUGH: G. Jeffrey Herndon, Branch Senior Scientist
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TO: Jim Tompkins/Vickie Walters, PM Team 25
Registration Division (RD) (7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of glyphosate in/on pasture and rangeland grasses, Roundup Ready® wheat, and nongrass animal feeds.

A summary of the findings and an assessment of human risk resulting from the proposed uses of glyphosate is provided in this document. The risk assessment, the residue chemistry data review, and the dietary risk assessment was provided by William Donovan (RAB1), the hazard characterization by William Dykstra (RAB1), the occupational/residential exposure assessment by Troy Swackhammer (RAB1), and the drinking water assessment by Pat Jennings of the Environmental Fate and Effects Division (EFED).

NOTE: HED recently completed a Section 3 risk assessment for the use of glyphosate on alfalfa hay and forage, field corn forage, stover and straw of the cereal grains crop group, and numerous minor crops (D267588, W. Donovan *et al.*, 17-AUG-2000). This document contains only those aspects of the risk assessment which are affected by the addition of the new uses of glyphosate in/on pasture and rangeland grasses, Roundup Ready® wheat, and nongrass animal feeds.

Recommendation for Tolerances and Registration

Provided that the petitioner submits revised Sections B and F, HED concludes that there are no residue chemistry or toxicology data requirements that would preclude the establishment of unconditional registrations for the new uses of glyphosate in/on pasture and rangeland grasses, Roundup Ready wheat, and nongrass animal feeds, and the following permanent tolerances for residues of glyphosate *per se* in/on:

Animal feed, nongrass, group	400 ppm
Grass, forage, fodder and hay, group	300 ppm
Wheat, forage	10 ppm
Wheat, hay	10 ppm
Wheat, grain	6.0 ppm

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1.0 EXECUTIVE SUMMARY

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).

Hazard Assessment

Glyphosate is of low acute toxicity following oral, dermal, and inhalation exposure, as evidenced by classification as Toxicity Category III or IV. Dermal sensitization results are negative. The requirement for an acute inhalation LC_{50} study was waived, since, based on physical properties ("wetcake"), the technical is not respirable. There was little systemic toxicity, usually consisting of clinical signs, decreased body weight and/or food consumption and, occasionally, liver and kidney toxicity, in several guideline studies conducted up to or greater than the limit dose of 1,000 mg/kg/day. There are no data gaps.

The NOAEL of 175 mg/kg/day for maternal toxicity based on mortality, diarrhea, and nasal discharge at the LOAEL of 350 mg/kg/day in the rabbit developmental study was the lowest NOAEL of all the major studies. These studies include the 24-month mouse carcinogenicity study (NOAEL = 750 mg/kg/day), the 1-year dog study (NOAEL = 500 mg/kg/day), the 2-year chronic toxicity/carcinogenicity rat study (NOAEL = 400 mg/kg/day), the 2-generation rat reproduction study (NOAEL = 500 mg/kg/day) and the rat developmental study (NOAEL = 1,000 mg/kg/day).

In a full battery of mutagenicity studies, glyphosate was negative for recombinant assay and reverse bacterial gene mutation assay, the in vivo cytogenetic assay, and the HGPRT/Chinese hamster cell assay. Based on these results, it is concluded that the mutagenic potential of glyphosate is negative.

On the basis of developmental studies in rats and rabbits and reproductive findings in rats, glyphosate exhibited no evidence of increased qualitative and quantitative susceptibility. A developmental neurotoxicity study was not required.

Dose Response Assessment

An acute reference dose (aRfD) was not established for any population subgroup or the general population, including infants and children, based on the absence of an appropriate toxicological endpoint attributable to a single exposure (dose), including maternal toxicity in developmental toxicity studies. The chronic reference dose (cRfD) was determined on the basis of maternal toxicity in the rabbit developmental toxicity study.

The HED Cancer Peer Review Committee classified glyphosate as a **"Group E"** chemical - negative for carcinogenicity in humans - based on the absence of evidence of carcinogenicity in male and female rats as well as in male and female mice.

The short-, and intermediate-term incidental, oral endpoints were 175 mg/kg/day both based on the maternal toxicity NOAEL of 175 mg/kg/day in the rabbit developmental study.

The short-, intermediate- and long-term dermal and inhalation endpoints were not selected based on the absence of hazard in the 21-day dermal toxicity study in rabbits and the 28-day inhalation toxicity study in rats. Additionally, there were no developmental or reproductive toxicity concerns relevant to the dermal and inhalation endpoint selection.

FQPA Decision: The Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) recommended that the 10x factor to account for enhanced sensitivity of infants and children be removed for all population subgroups and scenarios (HED Document Number 012584, B. Tarplee, 17-APR-1998).

Occupational Exposure and Risk Estimates
Based on the proposed use patterns, commercial handlers and grower/applicators are expected to have short-term dermal and inhalation exposures. However, since no short-term dermal or inhalation endpoints were selected by HIARC, no handler or occupational post-application assessment was conducted. The Roundup® Ultra and UltraMax labels specify that handlers must wear personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, and shoes with socks. The restricted entry interval (REI) on the Roundup® Ultra and UltraMax parent labels is 4 hours. The Pesticide Regulation (PR) Notice on the Reduced REI policy (95-03; 7-JUN-1995) confirms that glyphosate (isopropylamine salt) was identified as a candidate for the reduced REI of 4 hours. However, based on the existence of a developmental toxicity endpoint for glyphosate and that end-use products have acute Toxicity Classifications of I and II, **HED does not recommend glyphosate for a reduced REI.** An interim REI of 12 hours is appropriate under the Worker Protection Standard (WPS).

Dietary Exposure Estimates
A chronic dietary exposure analysis was conducted using the Dietary Exposure Evaluation Model (DEEM™, ver 7.73) and consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). The chronic analysis was based on very conservative assumptions (tolerance level residues, 100% crop treated, and DEEM™ default processing factors for rice and corn commodities). The chronic dietary food exposure estimate was less than HED's level of concern (<100% cPAD) for the general US population and all population subgroups (D280830,W. Donovan, 15-FEB-2002).

Non-Occupational (Recreational) and Residential Exposure and Risk Estimates
Glyphosate, isopropylamine salt is registered for use in recreational areas, including parks and golf courses for control of broadleaf weeds and grasses. It is also registered for use in lakes and

ponds, including reservoirs, for control of nuisance aquatic weeds. Based on the registered uses, adult and child golfers are anticipated to have short-term post-application dermal exposure at golf courses. Swimmers (adults, children and toddlers) are anticipated to have short-term post-application dermal and incidental ingestion exposures. However, since HIARC did not select dermal endpoints, no post-application dermal assessment is included; only a post-application incidental ingestion exposure assessment (swimmers) is included. Risk estimates for incidental ingestion by swimmers (adults, children and toddlers) ranged from 7,600 to 36,000.

Glyphosate, isopropylamine salt is also registered for broadcast and spot treatments on home lawns and gardens by homeowners and by lawn care operators (LCOs). Based on the registered residential use patterns, there is a potential for short-term dermal and inhalation exposures to homeowners who apply products containing glyphosate (residential handlers). Additionally, based on the results of environmental fate studies, there is also a potential for short- and intermediate-term post-application dermal exposures by adults and toddlers and incidental ingestion exposures by toddlers. However, since HIARC did not select short- or intermediate-term dermal or inhalation endpoints, no residential handler or post-application dermal assessment is included; only a post-application toddler assessment for incidental ingestion exposures is included. Risk estimates for toddler post-application incidental ingestion exposures ranged from 7,200 to greater than 10^6. All recreational and residential exposures assessed do not exceed HED's level of concern (MOEs <100).

Drinking Water

Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of glyphosate levels in surface and ground water were made using computer modeling. 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.

Exposure Scenarios and Risk Conclusions

Human health risk assessments were conducted for the following exposure scenarios: chronic dietary exposure (food only), aggregate chronic exposure (food and water), short/intermediate-term exposure (oral exposures from residential uses), and short/intermediate-term aggregate exposure (background chronic dietary exposure (food and drinking water) and short/intermediate-term oral exposures from residential uses). Other scenarios were not calculated since glyphosate has not been classified as a carcinogen, and there are no endpoints selected for acute dietary, dermal, or inhalation exposures. **All aggregate dietary exposures are below HED's level of concern.**

Recommendation for Tolerances and Registration

Provided that the petitioner submits revised Sections B and F, HED concludes that there are no residue chemistry or toxicology data requirements that would preclude the establishment of unconditional registrations for the new uses of glyphosate in/on pasture and rangeland grasses, Roundup Ready wheat, and nongrass animal feeds, and the following permanent tolerances for residues of glyphosate *per se* in/on:

Animal feed, nongrass, group	400 ppm
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Wheat, grain	6.0 ppm

2.0. HAZARD CHARACTERIZATION

2.1. Hazard Profile

Table 1. Acute Toxicity of GLYPHOSATE Technical

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	41400601	LD_{50} > 5,000 mg/kg	IV
81-2	Acute Dermal	41400602	LD_{50} > 5,000mg/kg	IV
81-3	Acute Inhalation	none	The Requirement for an Acute Inhalation LC_{50} Study was Waived	none
81-4	Primary Eye Irritation	41400603	Corneal Opacity or Irritation Clearing in 7 Days or Less	III
81-5	Primary Skin Irritation	41400604	mild or slight irritant	IV
81-6	Dermal Sensitization	41642307	not a sensitizer	none

Table 2. Toxicity Profile of Glyphosate Technical

Guideline No./Study Type	Results
870.3100 90-Day oral toxicity rodents- mouse	NOAEL = **1500** mg/kg/day in males and females LOAEL = **4500** mg/kg/day in males and females based on decreased body weight gain.
870.3100 90-Day oral toxicity rodents-rat (Range-finding)	LOAEL = **50** mg/kg/day in males and females based on possibly increased phosphorus and potassium values; **NOAEL** not established.
870.3150 90-Day oral toxicity in rodents- rat (Aminomethyl phosphoric acid - plant metabolite of glyphosate)	NOAEL = **400** mg/kg/day in males and females LOAEL = **1200** mg/kg/day in males and females based on body weight loss and histopathological lesions of the urinary bladder.
870.3485 28-Day inhalation toxicity- rat	NOAEL = **0.36** mg/L (HDT); LOAEL not established based on 6 hours/day, 5 days/week for 4 weeks.
870.3200 21-Day dermal toxicity- rabbit	NOAEL = **1000** mg/kg/day (males and females) LOAEL = **5000** mg/kg/day based on slight erythema and edema on intact and abraded skin of both sexes, and decreased food consumption in females.
870.3700a Prenatal developmental in rodents- rat	**Maternal** NOAEL = **1000** mg/kg/day LOAEL = **3500 mg/kg/day** based on inactivity, mortality, stomach hemorrhages and reduced body weight gain ***Developmental*** NOAEL = **1000** mg/kg/day LOAEL = **3500 mg/kg/day** based on increased incidence in the number of fetuses and litters with unossified sternebrae and decreased fetal body weight
870.3700b Prenatal developmental in nonrodents- rabbit	**Maternal** NOAEL = **175** mg/kg/day LOAEL = **350** mg/kg/day based on mortality, diarrhea, soft stools, nasal discharge. **Developmental** NOAEL = **350** mg/kg/day (HDT). LOAEL = not established.
870.3800 Reproduction and fertility effects-rat (3-generation)	**Parental/systemic NOAEL** = 30 mg/kg/day (HDT). **Reproductive NOAEL** = 30 mg/kg/day (HDT). **Offspring NOAEL** = 10 mg/kg/day. **Offspring LOAEL** = 30 mg/kg/day based on focal dilation of the kidney in male F3b pups.

Table 2. Toxicity Profile of Glyphosate Technical

Guideline No./Study Type	Results
870.3800 Reproduction and fertility effects-rat (2-generation)	**Parental/Systemic** NOAEL = **500** mg/kg/day in males and females LOAEL = **1500** mg/kg/day in males and females based on soft stools, decreased body weight gain and food consumption. Focal dilation of the kidney observed at 30 mg/kg/day in the 3-generation study was not observed at any dose level in this study. **Reproductive** NOAEL $\geq$ **1500** mg/kg/day (HDT) in males and females LOAEL = **not established.** **Offspring** NOAEL = **500** mg/kg/day in males and females LOAEL = **1500** mg/kg/day in males and females based on decreased body weight gain during lactation.
870.4100b Chronic toxicity dogs	NOAEL = **500** mg/kg/day in males and females (HDT) LOAEL = **not established.**
870.4300 Chronic/Carcino-genicity rats	NOAEL = **362** mg/kg/day in males, 457 mg/kg/day in females LOAEL = **940** mg/kg/day in males, 1183 mg/kg/day in females based on decreased body weight gain in females, decreased urinary pH in males, increased incidence of cataracts and lens abnormalities in males, and increased absolute and relative (to brain) liver weight in males. **No evidence of carcinogenicity**
870.4300 Carcinogenicity mice	NOAEL = **750** mg/kg/day in males and females LOAEL = **4500** mg/kg/day in males and females based on significant decreased body weight gain in both sexes, hepatocyte necrosis and interstitial nephritis in males, and increased incidence of proximal tubule epithelial basophilia and hypertrophy in the kidney of females. **No evidence of carcinogenicity**
870.5265 Gene Mutation	Non-mutagenic when tested up to 1000 ug/plate, in presence and absence of activation, in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537.
870.5300 Gene Mutation	Non-mutagenic at the HGPRT locus in Chinese hamster ovary cells tested up to cytotoxic concentrations or limit of solubility, in presence and absence of activation.
870.5385 In Vivo Cytogenetics - Bone Marrow	Non-mutagenic in rat bone marrow chromosome assay up to 1000 mg/kg in both sexes of Sprague Dawley rats.
870.5550 Rec- Assay and Gene Mutation Assay	There was no evidence of recombination in the rec-assay up to 2,000 ug/disk with B. subtilis H17 (rec+) and M45 (rec-). Negative for reverse gene mutation, both with and without S-9, up to 5,000 ug/plate (or cytotoxicity) with E. coli WP2hcrA and S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538.

Table 2. Toxicity Profile of Glyphosate Technical

Guideline No./Study Type	Results
870.7485 Metabolism and pharmacokinetics - rat	Absorption was 30-36% in males and females. Glyphosate was excreted unchanged in the feces and urine (97.5% minimum). The only metabolite present in the excreta was AMPA. Less than 1% of the absorbed dose remained in the carcass, primarily bone. Repeat dosing did not alter metabolism, distribution , and excretion.

Hazard Characterization

The existing toxicity database for glyphosate is adequate according to the Subdivision F Guideline requirements for a food-use registration. There are no data gaps. There is high confidence in the quality of the existing studies and the reliability of the toxicity endpoints identified for use in risk assessment.

Glyphosate is of low acute toxicity by oral, dermal, and ocular routes of exposure, since all studies are in Toxicity Category III or IV. Glyphosate is a mild skin irritant (Toxicity Category IV), and is not a dermal sensitizer in guinea pigs. There was no systemic toxicity in a 21 day dermal toxicity study in rats up to the limit dose (1,000 mg/kg/day). At the highest dose tested of 5,000 mg/kg/day, there was slight erythema and edema in intact and abraded skin of both sexes observed visually, but not microscopically, and decreased food consumption in females. There was no evidence of neurotoxicity in any of the toxicology studies conducted, and there are no data requirements for neurotoxicity studies. Since glyphosate lacks a leaving group, it would not seem likely to inhibit esterases, which is the presumptive neurotoxic mechanism of concern for all organophosphates (HIARC Doc. TXR#0050428, 22-JAN-02). An upper bound dermal penetration of 35% was estimated by the extrapolation method of comparing the maternal toxicity LOAEL of 350 mg/kg/day for the rabbit oral developmental toxicity study and the systemic NOAEL of 1,000 mg/kg/day in the 21 day dermal toxicity study.

In a full battery of mutagenicity studies, glyphosate was negative for recombinant assay and reverse bacterial gene mutation assay, the in vivo cytogenetic assay, and the HGPRT/Chinese hamster cell assay. Based on these results, it is concluded that the mutagenic potential of glyphosate is negative.

Glyphosate has been classified by the HED Cancer Peer Review Committee as **"a Group E"** chemical- **negative as a human carcinogen** - based on the absence of carcinogenicity in mice and rats (TXR#: 008898, 16-DEC-91). In the 2- year chronic toxicity/carcinogenicity rat feeding study, the results showed a slightly increased incidence of pancreatic islet cell adenomas in the low and high dose males; hepatocellular adenomas in the low and high dose males; and thyroid C-cell adenomas in the mid and high dose males and females. The Agency concluded that these adenomas were not treatment-related and glyphosate was not considered to be carcinogenic in

this study. The pancreatic islet cell adenomas did not display a positive dose-trend in their occurrence; there was no progression to carcinoma and the incidence of pancreatic hyperplasia was not dose-related. The hepatocellular adenomas were not statistically significant by pair-wise comparison; the incidence was within the range of historical controls; there was no progression to carcinoma and the hyperplasia was not compound-related. The C-cell adenomas were statistically significant by pair-wise comparison and were not dose-related; there was no progression to carcinoma and there was no significant dose-related increase in severity or incidence of hyperplasia in either sex.

In the 2-year carcinogenicity study in mice, the incidence in males of renal tubular adenomas, a rare tumor, was 1, 0, 1, and 3 in the control, low, mid, and high dose groups, respectively. Although the trend was significant, there was no statistical significance by pairwise comparison of the control and high dose group. The incidence at the high dose exceeded the occurrence of historical controls from the testing laboratory. The non-neoplastic findings in the male kidney did not occur in an increased dose-related manner and the tumorigenic findings in the kidney were considered to occur by chance rather than as a result of treatment.

The NOAEL of 175 mg/kg/day for maternal toxicity based on mortality, diarrhea, and nasal discharge at the LOAEL of 350 mg/kg/day in the rabbit developmental study was the lowest NOAEL of all the major studies. These studies include the 24-month mouse carcinogenicity study (NOAEL/LOAEL = 750/4500 mg/kg/day), the 1-year dog study (NOAEL = 500 mg/kg/day [HDT]), the 2-year chronic toxicity/carcinogenicity rat study (NOAEL/LOAEL = 362/940 mg/kg/day), the 2-generation rat reproduction study (NOAEL/LOAEL = 500/1500 mg/kg/day) and the rat developmental study (NOAEL/LOAEL = 1,000/3500 mg/kg/day).

In rats, developmental effects consisting of unossified sternebrae and decreased fetal body weight were observed at a LOAEL of 3,500 mg/kg/day which was also the LOAEL for maternal toxicity. The maternal NOAEL was 1,000 mg/kg/day based on mortality, decreased body weight gain, diarrhea, rales, inactivity, red matting on nose, mouth, forelimbs, and head, decrease in total implantations/dam and nonviable fetuses/dam. The developmental NOAEL was 1,000 mg/kg/day. In rabbits, the maternal NOAEL/LOAEL was 175/350 mg/kg/day based on increased mortality (does) and clinical signs. The developmental NOAEL was 350 mg/kg/day (HDT). In the 2-generation rat reproduction study, the offspring and parental NOAELs were 500 mg/kg/day based on decreased pup body weight during lactation (offspring) and soft stools, decreased body weight and food consumption (parents) at the LOAEL of 1500 mg/kg/day. The reproductive NOAEL was $\geq$ 1500 mg/kg/day (HDT).

In a three-generation rat reproduction study, the only effect observed in the study was an increased incidence of focal tubular dilation of the kidney (both unilateral and bilateral combined) in the high-dose male F_{3b} pups at 30 mg/kg/day (HDT). However, this effect (focal tubular dilation of the kidneys) was not observed at the 1500 mg/kg/day level in a subsequent 2-generation rat reproduction study. Therefore, the HED RfD/Peer Review Committee and the RARC concluded that the effect seen in the three generation study was a spurious rather than

glyphosate-related effect. Therefore, the NOAELs for parental, reproductive or offspring toxicity were ≥30 mg/kg/day.

In the rat metabolism study, absorption was estimated to be 30-36% in males and females. Glyphosate was excreted unchanged in the feces and urine (97.5% minimum). The only metabolite present in the excreta was small amounts of aminomethyl phosphonic acid (AMPA). Less than 1% of the absorbed dose remained in the carcass, primarily the bone. Repeated dosing did not alter metabolism, distribution, and excretion.

2.2. FQPA Considerations

On **March 26, 1998 and, again, on November 20, 2001** the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) met to examine the hazard data base and identify the acute dietary endpoints for Females 13-50 years old, as well as the General Population, the chronic reference dose (RfD), the endpoints for incidental oral exposure (on 20-NOV-01) and the toxicological endpoints selected for use as appropriate in occupational/residential exposure risk assessments based on redefined exposure periods (on 20-NOV-01) for glyphosate. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to glyphosate as required by the Food Quality Protection Act (FQPA) of 1996. The HIARC concluded the following:

- Based on the available data, there was no evidence of quantitative and qualitative increased susceptibility to *in utero* and/or postnatal exposure to glyphosate in rats or rabbits.

- Based upon a weight of evidence consideration (see discussion below), the Committee decided **not** to require the conduct of a developmental neurotoxicity study with glyphosate to evaluate the potential for developmental neurotoxic effects.

Evidence that support requiring a developmental neurotoxicity study:

None

Evidence that **does not** support a need for a Developmental Neurotoxicity study:

There was no evidence of neurotoxic clinical signs or neuropathology in any of the available studies.

There was no evidence of qualitative or quantitative increased susceptibility in rat and rabbit developmental studies or in the 2-generation rat reproduction study.

There was no additional information in the open literature.

The **FQPA Safety Factor Committee met on April 6, 1998** to evaluate the hazard and exposure data for glyphosate. The toxicology database for glyphosate is adequate according to the Subdivision F Guideline requirements for a food-use chemical. Acceptable developmental toxicity studies in the rat and rabbit are available, as is an acceptable 2-generation reproduction study in the rat. The HIARC concluded that a developmental neurotoxicity study with glyphosate is not required due to the absence of neurotoxicity in any study.

Based on the available data, there was no evidence of quantitative or qualitative increased susceptibility following *in utero* glyphosate exposure to rats and rabbits, or following pre/post natal exposure in the 2-generation reproduction study in rats.

The FQPA SFC concluded that the safety factor of 10x be removed (reduced to 1x) since there is no evidence of quantitative or qualitative increased susceptibility of the young demonstrated in the prenatal developmental studies in rats and rabbits and pre/post natal reproduction study in rats.

The Committee recommended that the **FQPA safety factor** of 10x be **removed** (reduced to 1x) because:

1) The toxicology data base is complete;
2) A developmental neurotoxicity study is **not** required; and
3) The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children.

2.3. Dose Response Assessment

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Dose and Endpoints for GLYPHOSATE Used 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 females 13-50 years old and general population	none	none	An acute dietary endpoint was not selected for the general population or females 13-50, since an appropriate endpoint attributable to a single exposure was not identified in the toxicology data base.
Chronic Dietary all populations	NOAEL= 175 mg/kg/day UF = 100 **Chronic RfD** = 1.75 mg/kg/day	FQPA SF = 1X **cPAD** = cRfD / FQPA SF = **1.75 mg/kg/day**	Developmental Toxicity Study - rabbit LOAEL = 350 mg/kg/day based on diarrhea, nasal discharge and death in maternal animals
Short-, and Intermediate-Term Incidental, Oral (Residential)	NOAEL = 175 mg/kg/day	LOC for MOE = 100	Developmental Toxicity Study - rabbit LOAEL = 350 mg/kg/day based on diarrhea, nasal discharge and death in maternal animals
Short-, Intermediate- and Long-Term Dermal (1 - 30 days, 1-6 months, 6 months - lifetime) (Occupational/ Residential)	none	none	Based on the systemic NOAEL of 1,000 mg/kg/day in the 21 day dermal toxicity study in rabbits, and the lack of concern for developmental and reproductive effects, the quantification of dermal risks is not required.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-, Intermediate- and Long-Term Inhalation (1-30 days, 1- 6 months, 6 months-lifetime) (Occupational/ Residential)	none	none	Based on the systemic toxicity NOAEL of 0.36 mg/L (HDT) in the 28-day inhalation toxicity study in rats, and the physical characteristics of the technical (wetcake), the quantification of inhalation risks is not required.
Cancer (oral, dermal, inhalation)	Cancer classification ("**Group E**")	Risk Assessment not required	No evidence of carcinogenicity

[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, LOC = level of concern, MOE = margin of exposure

Acute Dietary Endpoint: An acute reference dose (aRfD) for females 13-50 or the general population, including infants and children, was not selected because an acute oral endpoint attributed to a single-dose exposure could not be identified in any of the toxicology studies in the data base, including maternal toxicity in the developmental toxicity studies.

Chronic Dietary Endpoint: The chronic reference dose (cRfD) of 1.75 mg/kg/day was determined on the basis of the maternal toxicity NOAEL of 175 mg/kg/day in the rabbit developmental study. A UF of 100 (10-fold for interspecies extrapolation and 10-fold for intra species variability) was applied to the NOAEL of 175 mg/kg/day to derive the cRfD. The maternal toxicity NOAEL of 175 mg/kg/day is based on clinical signs and mortality seen at the LOAEL of 350 mg/kg/day in does. The NOAEL selected for establishing the chronic RfD (175 mg/kg/day) was observed to be lower than the NOAELs established in the long-term studies. Rabbits appear to be the most sensitive of the species tested. Though a developmental toxicity study was selected, the HIARC noted that the RfD is applicable to all population subgroups, since the endpoints of concern are maternal toxicity (not *in utero* effects), and these can occur in both males and females. The NOAEL selected however would be protective of other toxicity seen since they occurred at higher doses. The HIARC did not apply an additional safety factor for the use of the short term study for long term risk assessment because the weight of the evidence shows toxicity at much higher doses in other species and thus would provide adequate protection for long-term risk assessment. **The FQPA safety factor of 1X is applicable for chronic dietary risk assessment.** Therefore, the chronic population dose (cPAD) also equals

1.75 mg/kg/day.

Carcinogenicity: The HED Cancer Peer Review Committee classified glyphosate as a **"Group E"** chemical-**negative for carcinogenicity to humans-** based on the lack of evidence of carcinogenicity in mice and rats.

Short-, and Intermediate-Term Incidental, Oral Endpoints: The short-, and intermediate-term incidental, oral endpoints were selected to be 175 mg/kg/day based on the maternal toxicity NOAEL of 175 mg/kg/day in the rabbit developmental study. This NOAEL is based on clinical signs and mortality seen at the LOAEL of 350 mg/kg/day in does.

Short-, Intermediate- and Long-Term Dermal Endpoint: The short-, intermediate- and long-term dermal endpoints were not selected based on the absence of dermal hazard up to the limit dose of 1,000 mg/kg/day in the 21 day dermal toxicity study in rabbits.

Short-, Intermediate-, and Long-Term Inhalation Endpoints: The short-, intermediate-, and long-term inhalation endpoints were not selected based on the absence of inhalation hazard up to 0.36 mg/L (HDT) in the 28 day inhalation toxicity study in rats and the physical characteristics of the technical (wetcake).

2.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, glyphosate may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

3.0 EXPOSURE ASSESSMENT

A detailed review of the glyphosate residue chemistry database submitted in support of the proposed uses was recently completed (D265970, W. Donovan, 31-JAN-2002).

3.1 Summary of Proposed Uses

Pasture and Rangeland Grasses
Monsanto Company submitted a revision of the master label for the 3 lb ae/gal isopropylamine salt soluble concentrate/liquid (SC/L) formulation of glyphosate (Roundup® Ultra Herbicide; EPA Reg. No. 524-475) adding postemergent broadcast application to any grass in the Gramineae family except sugarcane, corn, and cereal grains, and including Bahiagrass, bermudagrass, bluegrass, brome, fescue, orchardgrass, ryegrass, timothy, and wheatgrass. In addition, the established spot treatment and wiper application uses, and preplant, preemergence, and pasture renovation uses were modified as noted below.

For postemergence use, the product is proposed for multiple broadcast applications at 0.28-1.5 lb ae/A to grasses, with a maximum seasonal application rate of 2.25 lb ae/A; neither a minimum retreatment interval (RTI) nor a pregrazing/preharvest interval (PGI/PHI) is specified. Applications may be made in 3-40 gal/A using ground equipment or in 3-15 gal/A using aerial equipment. Use of ammonium sulfate is not recommended when spraying rangeland grasses.

For spot treatment and wiper application, the use pattern has been modified as follows: for application rates >2.25 lb ae/A, no more than one-tenth of any acre should be treated at one time; and for application rates ≤2.25 lb ae/A, the entire field or any portion of it may be treated using these methods. Applications may be made in the same area at 30-day intervals. Domestic livestock must be removed prior to application, and a 7-day PGI/PHI interval is proposed.

For preplant, preemergence, and pasture renovation uses, the use pattern has been modified to specify a 0-day PGI/PHI for application rates ≤2.25 lb ae/A and a PGI/PHI of 56 days for application rates >2.25 lb ae/A. In addition, if applications total >2.25 lb ae/A, domestic livestock must be removed prior to application. The previously registered use directions reflected the more restrictive use pattern now specified for application rates >2.25 lb ae/A. A combined maximum seasonal rate resulting from all treatments is established at 6 lb ae/A.

Roundup Ready® Wheat
Monsanto Company submitted supplemental labeling for the 3 lb ae/gal isopropylamine salt SC/L formulation of glyphosate (Roundup® Ultra Herbicide; EPA Reg. No. 524-475) allowing broadcast preplant or preemergence, broadcast postemergence over-the-top and/or broadcast preharvest application to wheat with the Roundup Ready® gene. The petitioner noted that because Roundup Ready® wheat will initially be available only as selected spring wheat varieties, use is restricted to those states which represent the major spring wheat growing regions of the U.S.

The supplemental labeling restricts application of the 3 lb ae/gal SC/L formulation to Roundup Ready® wheat in the following states: ID, IL, IN, IA, KS, KY, MN, MO, MT, NE, ND, OH, OR, SD, WA, WI, and WY.

> For preplant or preemergence use, an unspecified number of preplant or preemergence applications are proposed at an unspecified individual application rate for a maximum combined application rate from all preplant or preemergence applications of 3.75 lb ae/A/season.

For postemergence over-the-top application, the product is proposed for up to two applications at 0.75 lb ae/A/application, made at emergence through the fifth-leaf stage of development, with a 10-day retreatment interval. The label proposes 7-, 30-, and 55-day PHIs for forage, hay, and grain, respectively following over-the-top applications.

For preharvest applications, the product is proposed for a single application at 0.75 lb ae/A made at the hard dough stage of grain (≤30% grain moisture), provided no more than 0.375 lb ae/A has been applied previously over-the-top.

A 7-day PHI for grain is proposed for preharvest use, and wheat stubble or straw may be grazed or fed immediately after harvest. Applications may be made in 5-20 gal/A (10-20 gal/A for preharvest applications) using ground equipment or in 3-15 gal/A using aerial equipment; applications made by aerial equipment are not to exceed 0.75 lb ae/A. The label contains the following statement regarding rotational crops: "There are no rotational crop restrictions following application of this glyphosate product."

Nongrass Animal Feeds

Monsanto Company submitted supplemental labeling for the 3.7 lb ae/gal isopropylamine salt SC/L formulation of glyphosate (Roundup® Ultramax Herbicide; EPA Reg. No. 524-512) allowing broadcast preharvest application to alfalfa and clover and other forage legumes, including kudzu, lespedeza, lupin, sainfoin, trefoil, velvet bean, vetch, crown vetch, and milk vetch.

The product is proposed for a single broadcast application at 1.5 lb ae/A for alfalfa or 1.16 lb ae/A for clover and other forage legumes. Use is limited to declining crop stands or any stand where crop destruction is acceptable. Use for crop grown for seed is prohibited. A 1.5-day PHI is proposed for alfalfa, and a 3-day PHI is proposed for clover.

Although the 3 lb/gal SC/L formulation of glyphosate (EPA Reg. No. 524-475) was used in the submitted field trials, the petitioner submitted supplemental labeling for the 3.7 lb ae/gal SC/L formulation (EPA Reg. No. 524-512). The petitioner stated that the new labeling is intended to allow all forage legumes to be treated in the same manner as alfalfa. Both labels support preplant, preemergence, and at-planting, and renovation (3.7 lb ae/gal only) applications to alfalfa, clover, and other forage legumes, and permit spot treatment or wiper application of glyphosate to alfalfa, clover and other forage legumes (3 lb ae/gal) or to alfalfa and clover only (3.7 lb ae/gal). The preharvest use directions which appear on the submitted label for alfalfa have already been approved on supplemental labels dated 10/5/2000 and 5/10/2001 for the 3 lb ae/gal and 3.7 lb ae/gal formulations, respectively. The preharvest use on clover and other forage legumes represents the only significant proposed change to the current labeling; the preharvest use pattern for alfalfa is presented for informational purposes.

On the submitted labeling, spot treatment and wiper applications have been expanded to include the other forage legumes in addition to alfalfa and clover. This is a house-keeping change for which no data are required; the proposed use already appears on the label for the 3 lb ae/gal SC/L formulation.

HED Conclusions: **The proposed use directions for grasses are not adequate. The petitioner should submit a revised Section B specifying a 0-day PGI and PHI for the proposed postemergence use on grass forage, and include a 30-day plant-back interval (PBI) for rotational crops.**

The proposed use directions for nongrass animal feeds are not adequate. The petitioner should submit a revised Section B specifying a 30-day PBI for rotational crops.

The proposed use directions for Roundup Ready® wheat are not adequate. The petitioner should submit a revised Section B stating that the maximum combined application rate is 4.875 lb ae/A/season when more than one type of application (preemergence, postemergence, or preharvest) is made, and include a 30-day PBI for rotational crops.

3.2 DIETARY EXPOSURE/RISK PATHWAY

3.2.1 RESIDUE PROFILE

Background: Permanent tolerances have been established for residues of glyphosate *per se* in/on a wide variety of crops as listed under 40 CFR 180.364.

Monsanto Company has submitted amended registration applications for 1) postemergence use of glyphosate (product name Roundup Ultra® Herbicide; EPA Reg. No. 524-475) on pasture and rangeland grasses, along with a petition to increase the tolerance for the grass forage, fodder, and hay group as a result of the proposed amended use, 2) glyphosate (product name Roundup Ultramax® Herbicide; EPA Reg. No. 524-512) use on nongrass animal feeds, along with a petition to establish a permanent crop group tolerance on nongrass animal feeds (forage, fodder, straw, and hay) group as a result of the proposed amended uses, and 3) expanded uses of glyphosate (product name Roundup Ultra® Herbicide; EPA Reg. No. 524-475) on Roundup Ready® wheat, along with a petition to establish permanent tolerances on wheat forage and hay as a result of the proposed amended uses.

As a result of the proposed new uses, the petitioner is proposing establishment of permanent tolerances for residues of glyphosate (N-(phosphonomethyl)glycine) *per se* resulting from the application of glyphosate, the isopropylamine salt of glyphosate, the ethanolamine salt of glyphosate and the ammonium salt of glyphosate in/on:

Animal feed, nongrass, group (Crop Group 18)	400 ppm
Grass, forage, fodder and hay, group (Crop Group 17)	300 ppm
Wheat, forage	10.0 ppm
Wheat, hay	10.0 ppm

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. Foliar-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, based on toxicological considerations, 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).

Metabolism studies submitted for genetically engineered glyphosate-tolerant canola (D242628, T. Bloem, 30-NOV-1998) and glyphosate-tolerant corn (D217539, G. Kramer, 14-MAR-1996) have indicated that metabolism in glyphosate-tolerant plants is essentially the same as that in normal plants. Thus, the terminal residue to be regulated in plants is glyphosate *per se*.

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 livestock 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). Thus, adequate analytical methods are available for residue data collection and enforcement of the proposed tolerances of glyphosate in/on the nongrass animal feed crop group; the grass forage, fodder, and hay crop group; wheat forage and hay; and livestock commodities.

Multiresidue Method (MRM)

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 the proposed uses.

Storage Stability Data

The maximum total storage intervals for grass, wheat, and alfalfa/clover samples were 11, 9.2, and 15 months, respectively. 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 at least 1 year, in livestock commodities for at least 2 years, and in water for at least 1 year (Memo, R. Perfetti, 27-OCT-1992). No additional storage stability data are needed, as the storage intervals for samples from the field trials are adequately supported by available storage stability data.

Crop Field Trials

Pasture and Rangeland Grasses

In thirteen trials (MRID 45089401) conducted in CA (1 trial), FL (1), IA (1), LA (1), NC (1), ND (1), NE (1), NY(1), TX (2), UT (1), WA (1), and WI (1), glyphosate residues were 94-286 ppm and 6.5-270 ppm in/on grass forage and hay, respectively, harvested 0 days (forage) or 3 days (hay; plus 1-4 days drying time) following a single broadcast application of the 3 lb ae/gal SC/L formulation and treated at ~2.25 lb ae/A, equivalent to 1x the proposed rate. The highest average field trial (HAFT) values for glyphosate residues were 267 and 259 ppm in/on grass forage and hay, respectively.

The crop field trials for glyphosate on grass forage and hay are classified acceptable and satisfy the guideline requirement for crop field trials. The proposed tolerance level of 300 ppm is adequate to cover residues of glyphosate *per se* in/on the grass, forage, fodder and hay, group (Crop Group 17).

Roundup Ready Wheat

In twenty-two field trials (MRID 45174701) conducted in the U.S. in MN (1 trial), MT (2), ND (2), and WA (1), and in Canada in AB (5 trials), MB (4), and SK (7), glyphosate residues were 0.028-9.14, <0.05-6.00, 0.014-5.62, and 0.019-71.8 ppm in/on Roundup Ready® wheat forage, hay, grain, and straw, respectively, harvested a minimum of 7 days (forage), 34 days (hay), and 6 days (grain and straw) following the final application of the 3 lb ae/gal SC/L formulation and treated at ~4.48 lb ae/A, equivalent to 1x the maximum proposed rate. The HAFT values for glyphosate residues were 8.78, 5.75, 4.71, and 71.5 ppm in/on wheat forage, hay, grain, and straw, respectively. The petitioner conducted four additional U.S. field trials in ND (1 trial), SD (2) and OR (1), for which results were not reported; one of the SD sites had been intended to serve as a residue decline trial site. In the ND and SD trials, samples were harvested but not analyzed because the field sites were infected with *Fusarium*. In the OR trial, several deviations occurred in the timing of applications and sampling stages that did not represent normal agronomic practices; thus, the trial was aborted before any grain or straw samples were harvested. Monsanto stated that Roundup Ready® wheat will initially be available only as selected spring wheat

varieties, and that therefore, residue sites were selected in the major spring wheat growing regions of the U.S. and Canada.

Although the number and geographical distribution of the wheat field trials does not conform to the recommendations listed in OPPTS 860.1500, in view of the reduced risk status of this petition and the limitation of the use to spring wheat growing areas of the U.S., HED is willing to classify the submitted field trial data as acceptable to satisfy the guideline requirement for field trials. However, HED emphasizes that the present determination applies to this action only and that for any expanded use to include winter wheat, further field trial data will be required to represent the regions in which winter wheat is typically grown. Based on the available data, HED concludes that residues of glyphosate in/on wheat straw will not exceed the established tolerance of 100 ppm for "grain, cereal, stover, and straw" group following application to Roundup Ready® wheat according to the proposed use patterns. Further, the data support increasing existing tolerance levels for wheat forage and hay to 10 ppm. However, the maximum glyphosate residue level in wheat grain, 5.6 ppm, exceeds the established tolerance level of 5.0 ppm. Accordingly, a tolerance level of 6.0 ppm is recommended to cover residues of glyphosate *per se* in wheat grain. **The petitioner should submit a revised Section F.**

Nongrass Animal Feeds
In ten field trials (MRID 45365401) conducted in AL (1 trial), CA (1), LA (1), MO (1), ND (2), NY (1), TX (2), and WI (1), glyphosate residues were 30.6-68.8 and 85.3-295.5 ppm in clover forage and hay, respectively, harvested 3 days following one application of the 3 lb ae/gal SC/L formulation and treated at 1.125 lb ae/A, equivalent to 1x the proposed rate. The HAFT values for glyphosate residues were 65.7 and 295.1 ppm in/on clover forage and hay, respectively.

Although no data reflecting application of glyphosate to alfalfa according to the proposed use pattern were submitted with this action, the petitioner cited the results of another alfalfa field trial study (MRID 43077001) in support of the group tolerance for nongrass animal feeds. In this study, residues of glyphosate were 48-158 ppm in/on alfalfa forage and 44-377 ppm in/on alfalfa hay harvested from 20 field trials 1 day following a single application of a 3 lb ae/gal SC/L formulation at ~1.5 lb ae/A, equivalent to ~1x the proposed rate; hay samples were field dried for 3-6 days prior to sample collection. The HAFT values for glyphosate residues were 152.7 and 340.7 ppm in/on alfalfa forage and hay, respectively. These data were presented in an Agency review of PP#4F4312/4H5692 for preharvest use of glyphosate on alfalfa (D201250, M. Rodriguez, 11-JAN-1995), and were recently found to be acceptable in connection with PP#9F05096 for increasing the preharvest use rate of glyphosate on alfalfa (D256740, W. Donovan, 09-JUN-2000).

The crop field trials for nongrass animal feeds (alfalfa and clover) are classified acceptable and satisfy the guideline requirement for crop field trials. Thus, a tolerance level of 400 ppm is recommended to cover residues of glyphosate *per se* in/on the animal feed, nongrass, group (Crop Group 18).

Processed Food/Feed
In the wheat processed food/feed study (MRID 45174701), the 3 lb ae/gal SC/L formulation

was applied to Roundup Ready® spring wheat three times (including one preemergence and two postemergence applications) at 3.79 lb ae/A (preemergence) and 0.75-0.76 lb ae/A/application (postemergence) for a total application rate of 5.30 lb ae/A (1.1x the maximum proposed seasonal rate for grain). The wheat grain was processed into flour, bran, middlings, shorts, germ, and aspirated grain fractions. Following treatment of wheat at 1.1x the maximum proposed seasonal rate for grain, detectable residues of glyphosate were observed at 4.13 ppm in wheat grain. The wheat was processed according to simulated commercial procedures into flour, bran, middlings, shorts, germ, and aspirated grain fractions. Analysis of the processed wheat fractions indicated that residues of glyphosate did not concentrate significantly in wheat flour, bran, middlings, shorts, and germ (concentration factors (CFs) of 0.93x, 1.33x, 0.89x, 1.02x, and 0.71x, respectively), but did concentrate up to 5.83x in wheat aspirated grain fractions.

The processed food/feed study is classified as acceptable and satisfies the guideline requirement for a processing study. Tolerances will not need to be established to cover residues of glyphosate in wheat processed commodities because residues in wheat flour, bran, middlings, shorts, and germ did not concentrate significantly and will be covered by the existing tolerance of 20 ppm for wheat, milling fractions (except flour), and residues in wheat aspirated grain fractions will be covered by the 50 ppm aspirated grain fraction tolerance recommended in a recent review (D265963, W. Donovan, 09-NOV-2000): HAFT X CF = 4.71 ppm X 5.83 = 27.5 ppm.

Meat, Milk, Poultry, Eggs

The current proposal to establish glyphosate tolerances at 300 and 400 ppm for crop groups 17 and 18, respectively, is not expected to result in an increase in the dietary burden for cattle, poultry, and hogs. Respective dietary burdens of 210 and 220 ppm were recently estimated for dairy and beef cattle, including a contribution from alfalfa hay as the roughage component of the diet with a tolerance of 400 ppm (D256740, W. Donovan, 09-JUN-2000). No impact is expected on the dietary burden to poultry or hogs since grass forage and hay are not feed items for these livestock, and the contribution from alfalfa was already considered.

Confined Accumulation in Rotational Crops

An acceptable confined rotational crop study was previously reviewed (Memo, A. Abramovitch, 10/14/92; MRIDs 41543201 and 41543202) which indicated that residues of glyphosate were not detectable in crops planted 30 days after treatment. The current label for glyphosate contains the following statement regarding rotational crops: "There are no rotational crop restrictions following application of this glyphosate product." However, in an HED review of Monsanto's proposal to remove a 30-day plantback restriction for crops on which use of glyphosate is not registered, HED concluded (D200041, G. Kramer, 12-MAY-1994) that the petitioner would be required to demonstrate that significant glyphosate residues would not be present in rotational crops planted 0 days after soil treatment, and recommended against the label amendment. No rotational crop data have been submitted in support of a 0-day plantback interval (PBI) for rotational crops; therefore, **the registrant should reinstate the 30-day PBI for crops on which use of glyphosate is not registered. A revised Section B should be submitted.**

International Harmonization of Tolerances

Codex and Mexican maximum residue limits (MRLs) are established for residues of glyphosate (glifosato) *per se* and Canadian MRLs are established for combined residues of glyphosate and AMPA in a variety of raw agricultural, processed, and animal commodities. Currently a relevant Codex MRL for hay or fodder (dry) of grasses is established at 50 ppm. No Canadian MRLs are established for any grass commodity. A Mexican MRL is established for pasture at 0.2 ppm. Because of the higher residue levels resulting from the proposed use pattern, harmonization of U.S. grass tolerances with existing Codex or Mexican MRLs is not possible.

For wheat related commodities, relevant Codex MRLs exist for: wheat grain at 5 ppm; unprocessed wheat bran at 20 ppm; wheat flour at 0.5 ppm; wheat wholemeal at 5 ppm; and straw and fodder (dry) of cereal grains at 100 ppm. Canadian MRLs are established for: wheat at 5 ppm and wheat milling fractions (excluding flour) at 15 ppm. A Mexican MRL is established for wheat at 5 ppm. The recommended tolerance level of 6.0 ppm for wheat grain slightly exceeds the Codex and Mexican MRLs, but by maintaining the wheat, milling fractions (excluding flour) tolerance at 20 ppm, harmony with international tolerances for wheat processed fractions can be maintained.

There are currently no Codex or Canadian MRLs established for glyphosate for any nongrass animal feed items. A Mexican MRL is established for alfalfa at 200 ppm. Harmonization with this level is not possible due to the higher residue levels found in the submitted field trial studies.

3.2.2 Chronic Dietary Exposure Analysis

The glyphosate chronic dietary exposure analysis was conducted using the DEEM™ software Version 7.73, which incorporates consumption data from USDA's CSFII, 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (*i.e.*, apple pie) are linked to raw agricultural commodities and their food forms (*i.e.*, apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM™ software. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment. No acute dietary analysis was conducted for glyphosate because no acute dietary dose/endpoint was identified by the HIARC (TXR No. 0050428, W. Dykstra, 22-JAN-2002).

For chronic dietary exposure and risk assessments, an estimate of the residue level in each food or food-form (*i.e.*, orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD for chronic exposure. This procedure is performed for each population

subgroup.

For chronic dietary risk, HED's level of concern is >100% cPAD. Dietary exposure estimates for representative population subgroups are presented in Table 4. The results of the chronic analysis indicate that the estimated chronic dietary risk associated with the proposed uses of glyphosate is below HED's level of concern.

Table 4. Summary of Results from Chronic DEEM ™ Analysis of Glyphosate.

Subgroup	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.031527	1.8
All Infants (< 1 year old)	0.062218	3.6
Children 1-6 years old	0.068016	3.9
Children 7-12 years old	0.045529	2.6
Females 13-50 years old	0.023477	1.3
Males 13-19 years old	0.031938	1.8
Males 20+ years old	0.026745	1.5
Seniors 55+ years old	0.022733	1.3

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, (*i.e.*, nursing and non-nursing infants or Hispanic females). Therefore, risks estimated for these population subgroups were included in representative populations as recommended by the Dietary Exposure Science Advisory Council (DESAC).

3.3 WATER EXPOSURE/RISK PATHWAY

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 glyphosate label allows multiple applications of 0.37 - 5 lbs ai/A up to a maximum of 10.6 lbs ai/A/year. 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, 12-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, 12-AUG-2000]. For comparison purposes, HED guidance suggests dividing the 56-day GENEEC EEC value by 3 ["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, 12-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 use in the chronic risk assessment.

3.4 NON-OCCUPATIONAL AND RESIDENTIAL EXPOSURE/RISK PATHWAY

Non-Occupational (Recreational) Exposures

Glyphosate, isopropylamine salt is registered for use in recreational areas, including parks and golf courses for control of broadleaf weeds and grasses. It is also registered for use in lakes and ponds, including reservoirs, for control of nuisance aquatic weeds. Based on the registered uses, the following exposures are anticipated:

- adult and child golfers, short-term post-application dermal exposure at golf courses.
- adult, child and toddler swimmers, short-term post-application exposure following applications to a lake or pond: dermal and incidental ingestion exposures

Since HIARC did not select dermal endpoints, no post-application dermal assessment is included; only a post-application incidental ingestion exposure assessment (swimmers) is included. It should noted however, that glyphosate is used for non-selective weed control on emersed aquatic weeds (see the U.S. Army Corps of Engineers' Aquatic Plant Control Center website at http://www.saj.usace.army.mil/conops/apc/weed_chem.htm#Use Guide). In this use pattern, it is unlikely that swimmers would be present in waterbodies with floating weeds present. Thus, the inclusion of the swimmer incidental ingestion exposure assessment is considered by HED to be conservative.

The exposure assumptions used in the swimmer assessment are based on HED's Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and

subsequent updates for swimming pools adapted for this assessment, but the Residential SOP assumptions are considered conservative for use in assessing this scenario as explained in Table 5.

Table 5. Comparison of Assumptions for Post-Application Swimmer Exposure Assessments for Glyphosate, Isopropylamine salt

Assumption	Residential SOP for Swimmers in Pools	Glyphosate Application: Post-Application in Lakes and Ponds
Post-application concentration	100% available concentration post-application	Very conservative assumption as applicators typically target foliage of emersed vegetation; actual product entering the top of the water column is anticipated to <<100%.
Duration of exposure	5 hours	5 hours assumed also, but considered conservative for a lake or pond
Inhalation exposure	Assumed for pool swimmers	No significant inhalation exposure is anticipated, since the formulation is non-volatile.

Based on the above qualifiers, the assumptions used in the swimmer assessment are summarized below:

- 100% of applied concentration available at maximum application rate in top one foot of water column.
- Ingestion rate: 0.05 L/hr.
- Exposure duration: 5 hrs/day (although a toddler is unlikely to be exposed for 5 hrs).
- Adult and toddler swimmers are included in this assessment as they are anticipated to represent the upper and lower bound of swimmer exposures. The respective body weights are 60 kg for adult-females (since NOAEL is based on developmental study) and 15 kg for toddlers.

Table 6 presents a summary of assumptions used to estimate the exposure to adult and toddler child swimmers and the corresponding risk estimates.

Table 6. Assumptions and Risk Estimates for Post-Application Swimmer Exposure Assessments for Glyphosate, Isopropylamine salt

Exposure Scenario	AR[1] (lb a.e./A)	Maximum Concentration in water (mg/L)[2]	Potential Dose Rate (PDR; oral mg/kg bw/day)[3]	Short-term MOE[4]
Incidental Oral Ingestion, Adult-female	3.75	1.38	0.00493	36,000

Table 6. Assumptions and Risk Estimates for Post-Application Swimmer Exposure Assessments for Glyphosate, Isopropylamine salt				
Incidental Oral, toddler			0.023	7,600

Notes

1. Application rate from registered labels for aquatic weed control using glyphosate IPA salt (ex. label = EPA Reg. No. 524-343; max rate = 7.5 pints/A containing 4 lb acid equivalent [ae] glyphosate/gal. x 1 gal./4 pints = 3.75 lb ae/A.
2. Maximum concentration in water (top 1 ft.) = 3.75 lb ae/A x 1A/43,560 ft^2 x 454,000 mg/lb x 1/ft x ft^3/28.32 L = 1.38 mg/L.
3. PDR, incidental oral exposure = concentration, C_w (mg/L) x ingestion rate, IgR (L/hr) x exposure time, ET (hrs/d) x 1/BW (adult-female=60 kg; toddler = 15 kg)
4. MOE = NOAEL/PDR; short-term incidental oral NOAEL = 175 mg/kg bw/d; The level of concern for adult females and toddlers for short-term, incidental oral exposures is MOEs < 100.

The MOEs presented in Table 6 for post-application exposure by swimmers to glyphosate in aquatic weed control applications are greater than 100 and do not exceed HED's level of concern for short-term non-occupational (recreational) exposures (MOEs < 100).

Residential Exposures

Glyphosate, isopropylamine salt is registered for broadcast and spot treatments on home lawns and gardens. Glyphosate products for homeowner use are packaged as ready-to-mix formulations and ready-to-use sprayers and are very common in home and garden stores in the U.S. Glyphosate products are also used by LCOs for broadcast and spot treatment weed control programs on homeowner lawns. Glyphosate products are also labeled for turf renovation (see http://www.monsanto.com/ito/products/round_pro.html for a step-by-step description of turf renovation). The following products are registered for residential lawn use, including lawn renovation (anticipated to represent the worst-case residential exposure):

- Roundup Pro™ (EPA Reg No. 524-475): soluble concentrate containing 41% glyphosate, maximum application rate = 1.5 lb ae/A
- Roundup ProDry™ (EPA Reg No. 524-505): formulation containing 71.4% glyphosate, maximum application rate = 1.62 lb ae/A

To characterize the persistence of glyphosate in the environment for this assessment, studies referenced in the Glyphosate RED, reported that half-lives in field studies (including soils) conducted in the coldest climates (i.e., Minnesota, New York and Iowa) were the longest and ranged from about 29 days up to about 140 days, indicating that glyphosate residues in the field are somewhat more persistent in cooler climates as opposed to milder ones (Georgia, California, Arizona, Ohio, and Texas). Also, glyphosate was shown to remain predominantly in the 0-6 inch soil layer at all field sites in one study.

Based on the registered residential use patterns, there is a potential for short-term dermal and

inhalation exposures to homeowners who apply products containing glyphosate (residential handlers). Additionally, based on the results of environmental fate studies, there is a potential for short- and intermediate-term post-application dermal exposures by adults and toddlers and incidental ingestion exposures by toddlers. However, since HIARC did not select short- or intermediate-term dermal or inhalation endpoints, no residential handler or post-application dermal assessment is included; only a post-application toddler assessment for incidental ingestion exposures is presented below.

The *SOPs For Residential Exposure Assessments*, Draft, 17-DEC-1997 and Exposure Science Advisory Committee (ExpoSAC) Policy No. 11, 22-FEB-2001: *Recommended Revisions to the SOPs for Residential Exposure* were used to estimate post-application incidental ingestion exposures and risk estimates for toddlers. The following assumptions were used to assess exposures to toddlers after contact with treated lawns:

- toddler body weight: 15 kg.
- toddler hand surface area is 20 cm^2, and a toddler performs 20 hand-to-mouth events per hour for short-term exposures.
- exposure duration: 2 hours per day.
- 5% of application rate represents fraction of glyphosate available for transfer to hands and a 50% saliva extraction factor for hand-to-mouth exposures.
- surface area of a object (for toddler object-to-mouth exposures) is approximately 25 cm^2.
- 20% of application rate available as dislodgeable residues for object-to-mouth exposures.
- 100% of application rate is available in the top 1 cm of soil for soil ingestion exposures. Also, it is assumed that a toddler can ingest 100 mg soil/d.

Table 7 provides a summary of the short- and intermediate-term risk estimates for post-application incidental ingestion exposures to toddlers.

Table 7: Summary of Toddler Incidental Ingestion Exposures and Risk Estimates for Residential Use of Glyphosate, Isopropylamine salt[1]

Activity	AR (lbs a.e./A)[2]	Residue Estimate[3]	PDR (mg/kg bw/d)[4]	Short-/Intermediate-term MOE[5]
Hand-to-mouth	1.62	DFR: 0.908 $\mu g/cm^2$	0.0242	7,200
Object-to-mouth		DFR: 3.63 $\mu g/cm^2$	0.00605	29,000
Soil Ingestion		Soil residue: 12.2 $\mu g/g$ soil	8.13×10^{-5}	$> 10^6$

Notes:

1. Sources: Standard Operating Procedures for Residential Exposure Assessments, Draft, December 17, 1997 and Exposure SAC Policy No. 11, Feb. 22, 2001: Recommended Revisions to the SOPs for

Residential Exposure.

2. AR = maximum application rate on Roundup ProDry label (EPA Reg. No. 524-505) for residential lawn treatment.
3. Residue estimates based on the following protocol from the Residential SOPs:
    a. Hand-to-mouth DFR = 1.62 lb ae/A x 0.05 x (4.54×10^8 μg/lb ae) x (2.47×10^{-8} A/cm^2) = 0.908 μg/cm^2.
    b. Object-to-mouth DFR = 1.62 lb ae/A x 0.20 x (4.54×10^8 μg/lb ae) x (2.47×10^{-8} A/cm^2) = 3.63 μg/cm^2.
    c. Soil Residue = 1.62 lb ae/A x fraction of residue in soil (100%)/cm x (4.54×10^8 μg/lb ae) x (2.47×10^{-8} A/cm^2) x 0.67 cm^3/g= 12.2 μg/g soil.
4. Potential Dose Rate (PDR; already normalized to body weight of toddler)
    a. Hand-to-mouth PDR = (0.908 μg/cm^2 x 0.50 x 20 cm^2/event x 20 events/hr x 10^{-3} mg/μg x 2 hrs/d)/15 kg = 0.0242 mg/kg bw/d .
    b. Object-to-mouth PDR = (3.63 μg/cm^2 x 25 cm^2/d x 10^{-3} mg/μg)/15 kg = 0.00605 mg/kg bw/d
    c. Soil Ingestion PDR = (12.2 μg/g soil x 100 mg soil/d x 10^{-6} g/μg)/15 kg = 8.13×10^{-5} mg/kg bw/d
5. MOE = NOAEL/PDR, where the short-term incidental oral NOAEL = 175 mg/kg/d HED's level of concern is for MOEs < 100 (short-term residential).

All MOEs calculated for post-application toddler exposures do not exceed the HED's level of concern for residential exposures (MOEs < 100).

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for glyphosate. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard air-blast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

4.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for the following: chronic aggregate exposure (food + water), and short/intermediate-term aggregate exposure (background chronic dietary exposure (food + water) and oral exposures from residential uses). Other scenarios were not evaluated because glyphosate has not been classified as a carcinogen and long-term occupational and residential exposures are not expected. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate

exposure, drinking water levels of concern (DWLOCs) were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate the acute and chronic DWLOCs, the dietary food estimates (from DEEM™) were subtracted from the appropriate PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

4.1 Acute Aggregate Risk (food + drinking water)

No acute aggregate risk analysis was conducted because the HIARC did not identify an acute dietary dose/endpoint (TXR No. 0050428, W. Dykstra, 22-JAN-2002).

4.2 Chronic Aggregate Risk (food + drinking water)

The chronic dietary exposure analysis assumed tolerance level residues, DEEM™ default processing factors, and 100% crop treated for all proposed commodities (Tier 1). The results of the chronic analysis indicate that the chronic dietary risk estimates for the general U.S. population and all population subgroups associated with the existing and proposed uses of glyphosate do not exceed HED's level of concern. The EECs generated by EFED are less than HED's DWLOCs. **Thus, chronic aggregate risk estimates are below HED's level of concern.** Table 8 summarizes the chronic aggregate exposure to glyphosate residues.

Table 8. Chronic Aggregate Exposures to Glyphosate Residues.

Scenario/ Population Subgroup	cPAD, mg/kg/day	Chronic Food Exposure, mg/kg/day	Maximum Chronic Water Exposure[1], mg/kg/day	Ground Water EEC, ppb	Surface Water EEC, ppb	Chronic DWLOC[2], ppb
U.S. Population	1.75	0.031527	1.718473	0.0038	230	60000
All infants (< 1 year old)	1.75	0.062218	1.687782	0.0038	230	17000
Children (1-6 years old)	1.75	0.068016	1.681984	0.0038	230	17000

Scenario/ Population Subgroup	cPAD, mg/kg/day	Chronic Food Exposure, mg/kg/day	Maximum Chronic Water Exposure[1], mg/kg/day	Ground Water EEC, ppb	Surface Water EEC, ppb	Chronic DWLOC[2], ppb
Children (7-12 years old)	1.75	0.045529	1.704471	0.0038	230	17000
Females (13-50 years old)	1.75	0.023473	1.726527	0.0038	230	52000
Males (13-19 years old)	1.75	0.031938	1.718062	0.0038	230	60000
Males (20+ years old)	1.75	0.026745	1.723255	0.0038	230	60000
Seniors (55+ years old)	1.75	0.022733	1.727267	0.0038	230	60000

[1] Maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM (mg/kg/day).

[2] The chronic DWLOCs were calculated as follows:

$$DWLOC\ (\mu g/L) = \frac{maximum\ water\ exposure\ (mg/kg/day)\ x\ body\ weight\ (kg)}{consumption\ (L/day)\ x\ 0.001\ mg/\mu g}$$

4.3 Short/Intermediate-Term Aggregate Risk (food + residential + water)

In aggregating short/intermediate-term risk, HED considered background chronic dietary exposure (food + water) and short/intermediate-term incidental oral exposures (see Tables 6 and 7). Because the incidental oral ingestion exposure estimates for toddlers from residential turf exposures (Table 7) exceeded the incidental oral exposure estimates from post-application swimmer exposures (Table 6), HED conducted this risk assessment using exposure estimates from just the worst-case situation. No attempt was made to combine exposures from the swimmer and residential turf scenarios due to the low probability of both occurring.

The total short/intermediate-term food and residential aggregate MOEs are 1800-2300. As these MOEs are greater than 100, the short/intermediate-term aggregate risk does not exceed HED's level of concern. For surface and ground water, the EECs of glyphosate are less than HED's DWLOCs for glyphosate in drinking water as a contribution to short/intermediate-term aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of glyphosate in drinking water do not contribute significantly to the short/intermediate-term aggregate human health risk at the present time. Table 9 summarizes the short/intermediate-term aggregate exposure to glyphosate residues.

Table 9. Short/Intermediate-Term Aggregate Risk and DWLOC Calculations.

Population	Short/Intermediate-Term Scenario									
	NOAEL mg/kg/day	Target MOE[1]	Max Exposure[2] mg/kg/day	Chronic Food Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]	Max Water Exposure[5] mg/kg/day	Ground Water EEC[6] (μg/L)	Surface Water EEC[6] (μg/L)	Short/Intermediate-Term DWLOC[7] (μg/L)
All Infants (<1 year)	175	100	1.75	0.062218	0.0303	1900	1.66	0.0038	230	17000
Children 1-6 years old	175	100	1.75	0.068016	0.0303	1800	1.65	0.0038	230	17000
Children 7-12 years old	175	100	1.75	0.045529	0.0303	2300	1.67	0.0038	230	17000

[1] Basis for the target MOE: inter- and intra-species uncertainty factors totaling 100.
[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE
[3] Residential Exposure = Oral exposure (see Table 7): sum of hand-to-mouth, object-to-mouth, and soil ingestion residue estimates.
[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]
[5] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)
[6] The glyphosate use producing the highest level was used.
[7] DWLOC(μg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/}\mu\text{g]}}$ (10 kg body weight assumed)

5.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance action for glyphosate because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of glyphosate. For purposes of this tolerance action, EPA has assumed that glyphosate does not have a common mechanism of toxicity with other substances.

On this basis, the registrant 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. If HED identifies other substances that share a common mechanism of toxicity with glyphosate, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at:
http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

6.0 OCCUPATIONAL EXPOSURE

Based on the proposed use patterns, commercial handlers and grower/applicators are expected to have short-term dermal and inhalation exposures. However, since no short-term dermal or inhalation endpoints were selected by HIARC, no handler or occupational post-application assessment was conducted. The Roundup® Ultra and UltraMax labels specify that handlers must wear personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, and shoes with socks.

6.1 Incidents

A search of OPP's REFS Incident Data Reporting System revealed a total of 3,950 records related to glyphosate. Adverse reactions in humans regarding glyphosate-only products primarily included skin and eye irritation, rashes, hives and nausea. From the RED, some glyphosate end-use products are in Toxicity Category I and II based on primary eye irritation or skin irritation. In California, where physicians are required to report pesticide poisonings, glyphosate was ranked third out of the 25 leading causes of illnesses or injury due to pesticides used between 1980 and 1984. These mixer/loader/applicator reported incidents consisted of eye and skin irritation. In reports issued by California since then (1987 and 1988), glyphosate continued to be a leading cause of illnesses or injuries (primarily eye and skin irritation).

6.2 Restricted Entry Interval (REI)

The REI on the Roundup® Ultra and UltraMax parent labels is 4 hours. The Pesticide Regulation (PR) Notice on the Reduced REI policy (95-03; 7-JUN-1995) confirms that glyphosate (isopropylamine salt) was identified as a candidate for the reduced REI of 4 hours (see note below).

Note: On January 11, 1995, EPA published a draft policy statement on "Reduced Restricted Entry Intervals for Certain Pesticides," in the Federal Register. The final policy was published in the Federal Register on May 3, 1995. In this policy, EPA permitted registrants to reduce the WPS interim REIs from12 to 4 hours for certain low risk pesticides. However, EPA included in this policy several tests that are key in the evaluation of continued eligibility for a reduced REI for glyphosate:

Regarding the active ingredient: There are no known reproductive, developmental, carcinogenic, or neurotoxic effects associated with the active ingredient.

> **Note:** The short- and intermediate-term incidental oral endpoints selected by HIARC were based on a maternal toxicity NOAEL from a developmental toxicity study in rabbits, where clinical signs and mortality were observed at 350 mg/kg/day.

Regarding the end-use product: The end-use product is in Toxicity Category III or IV for all of the acute toxicity studies: acute dermal, acute inhalation, primary skin irritation, and primary eye irritation.

Note: Per the RED, there are glyphosate end-use products are in Toxicity Category I and II based on primary eye irritation or dermal irritation.

Based on the above-described comparisons of the active ingredient, glyphosate and the end-use products with the Reduced REI candidate criteria, **HED does not recommend glyphosate for a reduced REI.** An interim REI of 12 hours is appropriate under WPS based on the acute toxicity for the active ingredient, glyphosate (as the isopropylamine salt) of Toxicity Category III for primary eye irritation and Toxicity Category IV for acute dermal and primary skin irritation.

7.0 DATA NEEDS/LABEL REQUIREMENTS

7.1 Chemistry

- *Section B:* Roundup Ready wheat label should state that the maximum combined application rate is 4.875 lb ae/A/season when more than one type of application (preemergence, postemergence, or preharvest) is made. The grass label should specify a 0-day PGI/PHI for the proposed postemergence use on grass forage. All labels (wheat, grass, and nongrass animal feeds) should include a 30-day PBI for rotational crops not registered for glyphosate.
- *Section F:* The existing glyphosate tolerance level of 5.0 ppm for wheat, grain should be increased to 6.0 ppm.

7.2 Toxicology

- None

7.3 Occupational Exposure

- The REI should be increased from 4 to 12 hours.

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