11-19-91

REVIEWER

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate (Roundup) - EPA Registration No. 524-308 - PP#8F3673 - Glyphosate in/on Corn - Tolerance Request and "Toxicology Profile"

Caswell No.: 661A
HED Project No.: 0-1393A
Record No.: 265528

FROM: William Dykstra, Ph. D.
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)

William Dykstra 11/19/91

THRU: Roger Gardner, Section Head
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)

Roger Gardner 11-19-91

TO: Robert J. Taylor, Product Manager 25
Registration Division (H7507C)

Requested Action

Tolerances are proposed for combined residues of the herbecide glyphosate (N-[phosphonomethyl]glycine) and its metabolite aminomethylphosphonic acid resulting from the application of the isopropylamine salt of glyphosate in or on the raw agricultural commodities of corn grain, forage and fodder at 2, 35 and 35 ppm, respectively. An increase in existing tolerances from a level of 0.5 ppm (40 CFR, 180.364) to 1 ppm in liver and kidney of cattle, goats, hogs, horses, and sheep has also been requested for the combined residues resulting from application of the isopropylamine and/or sodium sesqui salt.

Recommendations and Conclusions

1. Toxicology Branch I has no objections to the requested tolerances in/on corn grain, forage and fodder or liver and kidney of cattle, goats, hogs, horses, and sheep.

2. The reference dose (RfD) for glyphosate is 0.1 mg/kg/day and is based on a no-observed-effect level (NOEL) of 10 mg/kg /day which was established in the 3-generation reproduction study and an uncertainty factor of 100.

3. The Health Effects Division Carcinogenicity Peer Review Committee classified glyphosate as Group E (evidence of noncarcinogenicity for humans) (Dykstra and Ghali memorandum dated October 30, 1991).

4. There are no data gaps for the requested tolerance.

5. A Toxicology Profile is attached.

Toxicology Data Requirements

Use Pattern: Food **Last Updated:** 11/18/91
Test Substance: Technical grade glyphosate

Guide-line #	Type of Study	Required	Satisfied
81-1	Acute oral toxicity	Y	Y
81-2	Acute dermal toxicity	Y	Y
81-3	Acute inhalation toxicity	Y	W[1]
81-4	Primary eye irritation	Y	Y
81-5	Primary dermal irritation	Y	Y
81-6	Dermal sensitization	Y	Y
81-7	Acute delayed neurotoxicity	N	-
82-1	90-Day feeding		
	Rodent	Y	Y[2]
	Non-rodent	Y	Y[3]
82-2	21-Day dermal	Y	Y
82-3	90-Day dermal	N	-
82-4	90-Day inhalation	N	-
82-5	90-Day neurotoxicity		
	Hen	N	-
	Mammal	N	-
83-1	Chronic feeding		
	Rodent	Y	Y
	Non-rodent	Y	Y
83-2	Oncogenicity		
	Rat	Y	Y
	Mouse	Y	Y
83-3	Developmental toxicity		
	First species	Y	Y
	Second species	Y	Y
83-4	Multigeneration reproduction	Y	Y
84-2	Gene mutation	Y	Y
	Structural chromosomal aberration	Y	Y
	Other genotoxic effects	Y	Y
85-1	General metabolism	Y	Y
	Dermal penetration	N	-
	Domestic animal safety	N	-

Y = yes; N = no; W = waived; - = not applicable.

1 Waived because the Technical is a nonvolatile solid, handled as a wet cake [redacted]; adequate inhalation studies conducted on formulations indicate low degree of toxicity from this route; and people are not exposed to isopropylamine or sodium sesqui salts of glyphosate rather than the technical grade of the active ingredient.

Manufacturing Process information is not included

2 Satisfied by acceptable chronic feeding/oncogenicity studies in rats.

3 Satisfied by an acceptable long-term feeding study in dogs.

Toxicology Data Requirements

Use Pattern: Food Last Updated: 11/18/91
Test Substance: Roundup Herbicide (41.0% a.i.); EPA Reg. No. 524-308

Guide-line #	Type of Study	Required	Satisfied
81-1	Acute oral toxicity	Y	Y
81-2	Acute dermal toxicity	Y	Y
81-3	Acute inhalation toxicity	Y	Y[1]
81-4	Primary eye irritation	Y	Y
81-5	Primary dermal irritation	Y	Y
81-6	Dermal sensitization	Y	Y
81-7	Acute delayed neurotoxicity	N	-

Y = yes; N = no; W = waived; - = not applicable.

1 Satisfied by a study on another nearly identical formulation (EPA Reg. No. 524-UUL.

Toxicology Data Requirements

Use Pattern: Food Last Updated: 11/18/91
Test Substance: Roundup Herbicide (41.0% a.i.); EPA Reg. No. 524-UUL; similar to EPA Reg. No. 524-308, [redacted]

Guide-line #	Type of Study	Required	Satisfied
81-1	Acute oral toxicity	Y	Y
81-2	Acute dermal toxicity	Y	Y
81-3	Acute inhalation toxicity	Y	Y
81-4	Primary eye irritation	Y	Y
81-5	Primary dermal irritation	Y	Y
81-6	Dermal sensitization	Y	Y
81-7	Acute delayed neurotoxicity	N	-

Y = yes; N = no; W = waived; - = not applicable.

Commercial/financial information is not included

Toxicology Profile

Last Updated: 11/12/91

Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
81-1	Acute Oral Toxicity in Rats MRID 00067039 Study # Y-70-90 Date: 9/18/70 Acceptable	LD_{50} both sexes: 4320 mg/kg (3930 - 4750 mg/kg) TOXICITY CATEGORY: III Test material prepared as a 25.0% aqueous solution-suspension. Reduced activity and appetite, lethargy, diarrhea, increasing weakness, collapse and death.
81-2	Acute Dermal Toxicity in Rabbits MRID 00067039 Project # Y-70-90 Date: 9/18/70 Acceptable	LD_{50}: > 2.0 g/kg (both sexes) TOXICITY CATEGORY: IV Only 1 male and 1 female were used in study. No deaths, clinical signs or abnormal necropsy findings.
81-3	Acute Inhalation Toxicity in Rats	Waived. Agency accepted argument that the Technical is a nonvolatile solid, handled as a wet cake [redacted]; that adequate inhalation studies conducted on formulations indicate low degree of toxicity from this route and that people are not exposed to Technical - they would be exposed to isopropylamine or sodium sesqui salts of glyphosate.
81-4	Primary Eye Irritation in Rabbits Accession # 009856 Report # Y-70-90 Date: 9/18/70 Acceptable	Primary Irritation Score: 12.6/110 at 1 hour. TOXICITY CATEGORY: Not enough data in DER to tell - probably III or IV. Slight irritation.

Manufacturing process information is not included

Toxicology Profile

Last Updated: 11/12/91

Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
81-5	Primary Dermal Irritation in Rabbits Accession # 009856 Report # Y-70-90 Date: 9/18/70 Not rated	Primary Irritation Score: 0.0/8 (24 hour exposure) TOXICITY CATEGORY: IV No effects noted in DER
81-6	Dermal Sensitization in Guinea Pigs MRID: Not given Report # BD-83-008 Date: 7/22/83 Acceptable	Technical glyphosate was not a sensitizer under the conditions of the study.
81-7	Acute Delayed Neurotoxicity in Hens	No acceptable acute delayed neurotoxicity studies were available.
82-1 (a)	Subchronic Feeding in Rats (13 weeks) MRID 405594-01 Report # ML-86-351/EHL86128 Date: 11/30/87 Core Grade: Acceptable for range-finding	Effects: Levels tested: 0, 1000, 5000, 20000 ppm. This was a range-finding study. Male rats: possibly increased SP & K values at 1000 ppm and above; increased serum glucose at 5000 and 20000 ppm; increased serum BUN and AP at 20000 ppm; pancreatic lesions at 20000 ppm. Females: increased serum P and K at 1000 ppm and above. Does not appear to be a fully complete subchronic feeding, however, requirement fulfilled by rat chronic/oncogenicity feeding study.

Toxicology Profile

Last Updated: 11/12/91

Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
82-2	21-day dermal study in Rabbits MRID 00098460 Study # IRDC # 401-168 Date: 3/10/82 Core Grade: Guideline	NOEL: 1000 mg/kg/day LOEL: 5000 mg/kg/day Effects: Levels tested: 0, 100, 1000, 5000 mg/kg/day. Very slight erythema & edema observed visually but not microscopically (both sexes, intact & abraded skin); decreased food consumption; significant decrease in LDH.
83-1	Chronic feeding study in dogs Accession # 260021 Report # 830116; ML-83-137 Date: 8/22/85 Core Grade: Guideline	NOEL: > 500 mg/kg/day (HDT) Effects: Levels tested: 0, 20, 100, 500 mg/kg/day by capsule in Beagles. No effects were observed.
83-2 (a)	Oncogenicity study in mice Accession #'s 251007-014 Report # #BDN-77-420; Project # 77-2061 Date: 7/21/83 Core Grade: Minimum	Systemic NOEL: 5000 ppm Systemic LOEL: 30000 ppm Effects: Levels tested: 0, 1000, 5000, 30000 ppm for 18 months. Increased hepatocyte hypertrophy, hepatocyte necrosis, chronic interstitial nephritis in males; decrease in body weight in both sexes; increase in relative and absolute weight of testes and ovaries; proximal tubule epithelial basophilia and hypertrophy in females. Oncogenic NOEL (HDT): 30000 ppm (Assessed by Peer Review Committee).

Toxicology Profile

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Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
83-3	Teratology Study in Rabbits MRID 00046363 Study # IRDC # 401-056 Date: 2/29/80 Core Grade Minimum	Maternal NOEL: 175 mg/kg/day Maternal LOEL: 350 mg/kg/day Effects: Levels tested: 0, 75, 175, 350 mg/kg/day. Increased incidences of soft stool, diarrhea, nasal discharge and death (10 does died on day 21) Developmental NOEL: 350 mg/kg/day (HDT) Effects: No toxicologically significant signs of developmental toxicity at any dose level.
83-3	Teratology Study in Rats MRID 00046362 Study # IRDL 401-054 Date: 3/21/80 Core Grade Guideline	Maternal NOEL: 1000 mg/kg/day Maternal LOEL: 3500 mg/kg/day Effects: Dose levels tested: 0, 300, 1000, 3500 mg/kg/day. 28% decrease in body weight gain, diarrhea, soft stool, breathing rattles, inactivity, red matter in the region of nose, mouth, forelimbs or dorsal head and 6 deaths. Developmental NOEL: 1000 mg/kg/day Developmental LOEL: 3500 mg/kg/day Effects: Increase in number of litters and fetuses with unossified sternebrae and decrease in fetal body weight.

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Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
83-4	Multigeneration Reproduction Toxicity in Rats MRID 00105995 Project # 77-2063 (BDN-77-417) Date: 7/31/81 Core Grade Minimum	Parental NOEL: 30 mg/kg/day (HDT) Effects: Levels tested: 0, 3, 10, 30 mg/kg/day. Developmental NOEL: 10 mg/kg/day Developmental LOEL: 30 mg/kg/day Effects: Increased incidence of focal tubular dilation of the kidney (both unilateral and bilateral - combined) of male F_{3b} weanlings (pups). Reproductive NOEL: 30 mg/kg/day (HDT)
83-5	Chronic feeding study in rats MRID 00093879 Project # 77-2062 Date: 12/23/81 Core Grade: Minimum for chronic, supplementary for oncogenicity	Systemic NOEL: 31 mg/kg/day (HDT) Effects: Levels tested: 0, 3, 10, 31 mg/kg/day for 26 months. MTD not reached. Oncogenic NOEL: 31 mg/kg/day (HDT). Assessed by Peer Review Committee.
83-5	Chronic feeding study in rats MRID 416438-01 Study # MSL-10495 Date: 9/26/90 Core Grade: Guideline	Systemic NOEL: 8000 ppm Systemic LOEL: 20,000 ppm (HDT) Effects: Levels tested: 0, 2000, 8000, 20000 ppm (0, 100, 400, 1000 mg/kg/day). Decreased body weight and body weight gain in females, cataracts in males, decreased urinary pH in males, increased relative liver weight (to body) at 12 months, increased absolute and relative liver weights (to brain) at 24 months in males.

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Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
		Oncogenic NOEL: 20000 ppm (HDT) - assessed by Peer Review Committee.
84-2 (a)	Gene Mutation Assay (Ames Test) MRID 00078620 Study # LF-78-161 Date: 6/16/78 Acceptable	Tested with and without metabolic activation from 0.1 - 1000 µg/plate. No increase in reverse mutations were observed at any dose level. Positive controls produced expected positive results.
84-2 (a)	Gene Mutation Assay (Mammalian Cell) MRID 00132681 Study # ML-83-155; EHL 830079 Date: 10/20/83 Acceptable	Tested from 2 - 25 mg/ml. No mutagenic response was observed either with or without S-9, up to limit of cytotoxicity.
84-2 (b)	Structural Chromosomal Aberration Assay (Cytogenetics In Vivo) MRID 00132683 Study # ML-83-236 Date: 10/20/83 Acceptable	Glyphosate was administered i.p. at 1 g/kg in 10 ml/kg. No significant clastogenic effects were observed under conditions of study. No fatalities or other signs of toxicity were observed. Positive controls produced expected positive results.
84-2 (c)	Other Genotoxicity Assays (Rec-Assay in B. subtilis) MRID 00078619 Study # None Date: 7/20/78 Acceptable	Tested from 20 - 2000 µg/disk in rec-assay using B. subtilis H17 (rec^+) and M45 (rec^-) and from 10 - 5000 µg/plate in reverse mutation assays employing E. coli WP2 hcr and Salmonella typhimurium. No increases in mutations were observed at any dose level.

Toxicology Profile

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Technical Grade Glyphosate

Guide-line #	Study Identification and Classification	Results
85-1	Metabolism MRID 407671-01 and 02 Report # MSL-7215; MSL7206 Date: 3/23/88 Acceptable	30-36% of orally administered glyphosate is absorbed. Glyphosate is excreted unchanged in the feces and urine (97.5% minimum). The only metabolite formed is AMPA (found at levels of 0.2 - 0.4% in urine and feces). Less than 1% of the absorbed dose remained in the tissues and organs, primarily bone. Repeated dosing at 10 mg/kg does not significantly alter the metabolism, distribution, or excretion of glyphosate.
85-1	Metabolism MRID 00132685 Study # 830109; DMEH # ML-83-218 Date: 10/24/83 Acceptable	30 minutes following i.p. injection of [^{14}C]-glyphosate to rats at 1150 mg/kg, the concentration of radiolabel present in bone marrow was 267 +/- 31 and 413 +/- 39 ppm, respectively (equivalent to 0.0044 and 0.0072 % of dose). Assuming first order kinetics, the decrease in radioactivity occurred with a half-life of 7.6 and 4.2 hours from the males and females, respectively. Similarly, the half-lives of radiolabel in plasma were approximately 1 hour in both sexes.

Toxicology Profile

Last Updated: 11/12/91

41.0% Formulation Roundup Herbicide (EPA Reg. No. 524-308)

Guide-line #	Study Identification and Classification	Results
81-1	Acute Oral Toxicity in Rats MRID 241301 Project # 4884-77 Date: 5/16/79 Acceptable	LD_{50}: 5.4 g/kg (4.6-6.29 g/kg 95% C.L.; both sexes) TOXICITY CATEGORY: IV Necropsies revealed dark lungs, liver, kidneys & spleen.
81-2	Acute Dermal Toxicity in Rabbits MRID 241301 Project # 4885-77 Date: 1/17/79 Acceptable	LD_{50} > 5 g/kg (both sexes) TOXICITY CATEGORY: IV No deaths.
81-3	Acute Inhalation Toxicity in Rats MRID Report # Date:	Study not available. Study is available on nearly identical formulation (524-UUL).
81-4	Primary Eye Irritation in Rabbits MRID 416893-01 Report # BD-90-314 Date: 12/11/90 Acceptable	Primary Irritation Score: Corrosive TOXICITY CATEGORY: I (Danger) Pannus, ulceration, corneal opacity, conjunctivitis persisting until day 21.
81-5	Primary Dermal Irritation in Rabbits MRID 241301 Project # 4886-77 Date: 8/6/79 Unacceptable	Primary Irritation Score: 0.1/4.0 TOXICITY CATEGORY: IV Test material was diluted.

Toxicology Profile

Last Updated: 11/12/91

41.0% Formulation Roundup Herbicide (EPA Reg. No. 524-308)

Guide-line #	Study Identification and Classification	Results
81-6	Dermal Sensitization in Guinea Pigs MRID Report # Date: Acceptable/Unacceptable	Study not available. Study is available on nearly identical formulation (524-UUL).

Toxicology Profile

Last Updated: 11/12/91

41.0% Formulation Roundup Herbicide (EPA Reg. No. 524-UUL)
(identical to 41.0% Roundup Formulation EPA [redacted] Reg. No. 524-308 except

Guide-line #	Study Identification and Classification	Results
81-1	Acute Oral Toxicity in Rats MRID 416423-02 Report # SB-90-191 Date: 9/6/90 Acceptable	LD_{50} > 5.0 g/kg (both sexes) TOXICITY CATEGORY: IV No deaths.
81-2	Acute Dermal Toxicity in Rabbits MRID 416423-03 Report # SB-90-192 Date: 9/6/90 Acceptable	LD_{50} > 5.0 g/kg (both sexes) TOXICITY CATEGORY: IV No deaths.
81-3	Acute Inhalation Toxicity in Rats MRID 416423-06 Report # EHL90073 Date: 8/24/90 Acceptable	LC_{50}: 2.5 (1.7-3.9) mg/l (males) LC_{50}: 2.6 (2.1-3.3) mg/l (females) (Four hour exposure) TOXICITY CATEGORY: III Symptoms during exposure: include hypoactivity and labored respiration; toxic signs include corneal opacity and hair loss.
81-4	Primary Eye Irritation in Rabbits MRID 416423-04 Report # FD-90-120 Date: 5/15/90 Acceptable	Primary Irritation Score: Not calculated in DERs TOXICITY CATEGORY: Generally III No corneal opacity. 7 eye studies tested in various labs. The following categories were calculated: Supplementary (III), II, III, III, III, Supplementary (III).

Commercial / Financial information is not included

Toxicology Profile

Last Updated: 11/12/91

41.0% Formulation Roundup Herbicide (EPA Reg. No. 524-UUL)
(identical to 41.0% Roundup Formulation EPA Reg. No. 524-308 except [redacted]

Guide-line #	Study Identification and Classification	Results
81-5	Primary Dermal Irritation in Rabbits MRID 416423-05 Report # SB-90-193 Date: 8/15/90 Acceptable	Primary Irritation Score: 0.38-4.00 TOXICITY CATEGORY: IV
81-6	Dermal Sensitization in Guinea Pigs MRID 416423-07 Report # BD-90-203 Date: 8/17/90 Acceptable	The test substance is not a sensitizer.

Commercial/financial information is not available

Data Gaps: None.

Actions Being Taken to Obtain Additional Information or Clarification: N/A

Reference Dose (RfD):

The recommended RfD (to the RfD Workgroup) is 0.10 mg/kg/day. This value was calculated by using the 3-generation reproduction study NOEL of 10.0 mg/kg/day and a safety factor of 100. This RfD has been verified or approved by a Health Effects Division and Agency RfD Committee.

Pending Regulatory Actions: None

Toxicologic Issues Pertinent to This Request: There are no toxicologic issues pertinent to this request. However, the following 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 March 4, 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, 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 February 11-12, 1986 (report dated February 24, 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 comparision of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisions 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 second rat study was conducted and HED deferred a decision on the repeat of an additional mouse oncogenicity study until the second rat feeding study had been evaluated by the Peer Review Committee.

The Health Effects Division Carcinogenicity Peer Review Committee convened on June 26, 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 (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 Peer Review Committee 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 Peer Review Committee concluded that the renal tubular neoplasms in high dose male mice were not compound-related.

The Toxicology Branch (TB-I) has concluded that the N-nitrosoglyphosate (NNG) content of glyphosate is not toxicologically significant (memorandum of W. Dykstra dated November 5, 1987) and that the levels of N-nitrososarcosine (NSAR) and N-nitro-N-methylaminomethylphosphonic acid (NNMAMP) in Polado^{R} are not of toxicological concern (memorandum of W. Dykstra dated April 26, 1988). The carcinogenic risks to workers from the 1,4-dioxane impurity in the herbicide surfactant are less than 10^{-6}.