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SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: March 13, 2002

SUBJECT: Occupational (and Updated Non-Occupational and Residential) Exposure Risk Assessment for the Use of **Glyphosate, Isopropylamine salt** on Alfalfa, Clover and other Forage Legumes, Roundup Ready® Wheat and Corn, Grass forage, Fodder, and Hay. PC Code: 103601; DP Barcode: D281503

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Introduction

The Registration Division has requested that the Health Effects Division (HED) assess the potential occupational and residential exposures resulting from the proposed new uses of glyphosate, isopropylamine salt (N-phosphonomethyl glycine; parent labels: RoundUp® Ultra and UltraMax, EPA Reg. No. 524-475 and 524-512, respectively) on alfalfa, clover and other forage legumes, Roundup Ready® wheat and corn, grass forage, fodder, and hay. A Reregistration Eligibility Decision (RED) was completed for glyphosate in September 1993 (EPA 738-R-93-014). The risk estimates in this assessment are based on updated toxicological endpoints identified by HED's Hazard Identification Assessment Review Committee (HIARC) in a meeting held on November 20, 2001. At this meeting, the HIARC selected the incidental oral endpoint of 175 mg/kg/day for short- and intermediate term exposures. HIARC did not select dermal or inhalation endpoints (see Attachment A for summary of acute toxicity and toxicological endpoints for glyphosate).

Additionally, HIARC confirmed that durations for any short-, intermediate-, and long-term exposures and associated endpoints were extended to the following based on changes to HED's exposure duration policy (see HED Hot Sheet #17, 04-JUN-2001):

- Short-term exposure duration, defined as lasting from 1 day to 1 month
- Intermediate-term exposure duration, defined as lasting from 1 to 6 months
- Long-term exposure duration, defined as lasting longer than 6 months

The carcinogenic potential of glyphosate was evaluated by the HED Cancer Peer Review Committee on March 26,1998 and was classified as a Group E chemical -- no evidence of carcinogenicity for humans in two acceptable animal studies. The HED FQPA Safety Factor Committee met on April 6, 1998 to evaluate the hazard and exposure data for glyphosate and recommended that the FQPA Safety Factor be removed in assessing the risk posed by this chemical (see HED DOC. NO. 012584).

Conclusions

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 end-use products examined for these new uses (Roundup® Ultra and UltraMax) meet the criteria for a 4-hour restricted entry interval (REI), since the active ingredient has no known reproductive, developmental, carcinogenic, or neurotoxic effects and the end-use products are in Toxicity Category III or IV for the acute criteria. However, HED recommends that any other end-use products that are in Toxicity Category I or II for the acute criteria have a 12-hour REI specified on the label.

Additionally, since there are registered products that result in residential and non-occupational exposures, this assessment presents the risk estimates for recreational and residential exposures related to incidental ingestion only as a result of the selection of incidental oral endpoints by HIARC. Based on the registered use patterns, swimmers are anticipated to have short-term post-application incidental oral exposures from aquatic uses and toddlers are anticipated to have short-term post-application incidental oral exposures from hand-to-mouth behavior to treated lawns. Risk estimates for swimmers (adults, children and toddlers) ranged from 7,600 to 36,000; risk estimates for toddlers 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).

Summary of Proposed Occupational Use Patterns

Glyphosate is a systemic herbicide that can be applied before, during or after planting prior to crop emergence to control annual and perennial weeds and woody brush and trees, based on the parent and proposed supplemental labels. Applications may be made any time of the year. Aerial and ground broadcast applications and spot and wiper treatments are allowed. Table 1 provides a summary of the proposed occupational uses of glyphosate for this action.

Table 1. Proposed New Occupational Use Patterns for Glyphosate, Isopropylamine salt				
Crops/Use Site	Alfalfa, Clover and other Forage Legumes	Roundup Ready® Wheat	Roundup Ready® Corn	Grass forage, Fodder, and Hay
Formulation	RoundUp® Ultra Max EPA 524-512, water-soluble liquid; 50.2% glyphosate as isopropylamine salt; 3.7 lbs as acid equivalent (ae)	RoundUp® Ultra EPA Reg. No. 524-475, water-soluble liquid; 41% glyphosate as isopropylamine salt, 3 lbs as acid equivalent (ae)		
Used by	Commercial applicators, private growers			
Application methods	Ground broadcast applications	Aerial and ground broadcast applications, spot treatment, and wiper applications		
Maximum application rate (lb active ingredient as acid equivalent [ae]/A)	alfalfa: 1.5 lb ae/A; clover and other forage legumes: 1.16 lb ae/A	0.75 lb ae /A	0.75 lb ae/A	2.25 lb ae/A
Max Number of Applications	One preharvest application per season	No more than 3.75 lb ae/A per season	No more than 1.5 lb ae/A per growing season	No more than 2.25 lb ae/A per year
Timing and frequency of applications	Allow 30 d between spot treatment or wiper applications	Allow 10 d between applications	Allow 10 d between applications	Allow 30 d between applications
PHI	36 hr for alfalfa; 3 d for clover and other forage legumes	55 d for wheat grain; 7d for harvest or feeding of wheat forage	50 d for corn forage; 7 d for corn grain	7 d for grazing or harvesting after spot or wiper treatment; 8 weeks after preplant, pre-emergence or pasture renovation;

Occupational Exposure and Risk Assessment/Characterization

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.

a. 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

dermal irritation. The RED referenced California incident reports where physicians are required to report pesticide poisonings. In the California reports, glyphosate was ranked third out of the 25 leading causes of illnesses or injury due to pesticides used between 1980 and 1984; these reported incidents involved mixer/loader/applicators and consisted of eye and skin irritation.

Per the RED, the Agency recommended personal protective equipment in the 1986 Registration Standard, including protective eyewear for mixer/loader/applicators using end-use products that could cause eye or skin irritation. At that time, it was determined that mixer/loaders were at risk of eye or skin injury from splashes during mixing and loading. The Agency did not require personal protective equipment for users of "homeowner" products (containing up to 10% glyphosate) because of the low concentration of glyphosate and because the products are "ready-to-use", requiring no mixing; therefore, the potential for eye or dermal exposure is minimized. The Agency, did not at the time the RED was completed, add any additional personal protective equipment requirements to the labels of end-use products; however, any existing personal protective equipment on those labels must be retained.

b. 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; 3-MAY-1995) confirms that glyphosate (isopropylamine salt) was identified as a candidate for the reduced REI of 4 hours. 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 Worker Protection Standard (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 continued evaluation of eligibility for glyphosate:

- *Regarding the active ingredient:* The policy stipulates that there must be no known reproductive, developmental, carcinogenic, or neurotoxic effects associated with the active ingredient. 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. This effect was not interpreted as a development effect by HIARC (personal communication with J. Rowland, HED, 12-MAR-2001). Additionally, no reproductive, carcinogenic or neurotoxic effects were identified by HIARC. Thus, the active ingredient remains an eligible candidate for a 4-hr REI.

- *Regarding the end-use product:* The policy stipulates that the end-use product must be 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 that the end-use products in this action appear to remain eligible for the 4-hour REI. However, HED recommends that any end use products that are Toxicity Category I or II for the acute criteria have a 12-hour REI specified on the label.

Non-Occupational (Recreational) Exposure Risk Assessment/Characterization

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. 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 2.

Table 2. 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 for (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 adults and 15 kg for toddlers.

Table 3 presents a summary of assumptions used to estimate the exposure to adult and toddler child swimmers and the corresponding risk estimates.

Table 3. Assumptions and Risk Estimates for Post-Application Swimmer Exposure Assessments for Glyphosate, Isopropylamine salt

Exposure Scenario	AR[1] (lb a.e./A)	Concentration in water (mg/L)[2]	Potential Dose Rate (PDR; oral)[3]	Short-term MOE[4]
Incidental Oral Ingestion, Adult	3.75	1.38	0.00493	36,000
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 x **4 lb acid equivalent [ae]** glyphosate/gal. x 1 gal./8 pints = 3.75 lb ae/A.
2. 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 3 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 Exposure Risk Assessment/Characterization

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 lawn care operators (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™ (524-475): soluble concentrate containing 41% glyphosate, maximum application rate = 1.5 lb ae/A
- Roundup ProDry™ (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.
- The surface area of a toddler's hand 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/d.

Table 4 provides a summary of the short- and intermediate-term risk estimates for post-application incidental ingestion exposures to toddlers.

Table 4: Summary of Toddler Incidental Ingestion Exposures and Risk Estimates for Residential Use of Glyphosate, Isopropylamine salt[1]

Activity	Application Rate (AR; lbs a.e./A)[2]	Residue Estimate[3]	Potential Dose Rate (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 $\mu g/cm^2$.
   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 $\mu g/cm^2$.
   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 $\mu g/g$ soil.
4. Potential Dose Rate (PDR; already normalized to body weight of toddler)
   a. Hand-to-mouth PDR = (0.908 $\mu g/cm^2$ 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 $\mu g/cm^2$ x 25 cm^2/d x 10^{-3} mg/μg)/15 kg = 0.00605 mg/kg bw/d
   c. Soil Ingestion PDR = (12.2 $\mu g/g$ 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).

cc: Chemical file, D. Vogel, T. Swackhammer
Peer Reviews: ORE Team (01/23/02), ExpoSAC (01/31/02), RAB1 (02/13/02)

Attachment A: Summary of Acute Toxicity and Toxicological Endpoints for Glyphosate, Isopropylamine salt

Acute Toxicity of GLYPHOSATE

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

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
An Acute Dietary endpoint for females 13-50 or the general population was not selected	NOAEL= none UF = none	An acute dietary endpoint was not selected, since an effect attributable to a single dose/exposure was not identified in the data base.	none
	Acute RfD = not selected		
Chronic Dietary	NOAEL = 175 UF = 100	Maternal toxicity NOAEL in rabbits based on clinical signs and mortality at 350 mg/kg/day	Developmental toxicity study in rabbits
		Chronic RfD = 2.0 mg/kg/day	
Incidental Oral, Short-, and Intermediate-Term	NOAEL= 175	Maternal toxicity NOAEL in rabbits based on clinical signs and mortality at 350 mg/kg/day	Developmental toxicity study in rabbits
Dermal, Short-, Intermediate-, and Long-Term	NOAEL= none	Based on the absence of systemic effects up to 1,000 mg/kg/day in a 21 day dermal toxicity study in rabbits, a dermal hazard was not identified.	None selected
Inhalation, Short-, Intermediate-, and Long-Term	NOAEL= none	Based on the absence of inhalation effects in a 28 day inhalation study and the wetcake property of technical glyphosate, an inhalation hazard was not identified.	None selected

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