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

MEMORANDUM AUG 20 1982

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Don Stubbs (41)
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)
and
John W. Melone, Acting Director
Hazard Evaluation Division (TS-769)

SUBJECT: Crisis exemption for the use of Glyphosate in wheat in the state of Oregon. Section 18 - 82-OR-19, Action Code 550, EPA Reg. No. 524-308-AA

Recommendation:

1. The crisis exemption for the use of glyphosate on wheat in the state of Oregon can be toxicologically supported.

2. Chronic oral toxicity data in a non-rodent species is a data gap, and the status of subchronic data in a non-rodent is unclear.

Review:

1. Action Requested:

The state of Oregon has requested a crisis exemption for use of Glyphosate (Roundup®) herbicide for control of common rye in commercial wheat fields in eastern Oregon; the crisis was to begin at noon June 2, 1982.

One gallon of Roundup® was to be mixed in 2 gallons of water to prepare a 33% solution, one gallon of which will treat 50 acres of wheat. This is equivalent to 2.0 oz of Roundup®/acre or 0.08 lbs. active ingredient/acre.

Immediate treatment of 250,000 rye-infected wheat acres in eastern Oregon was judged essential, this acreage required 5,000 gallons of Roundup.

Roundup® was to be applied with use of a rope wick or other wiper applicator to rye after it had headed. The lowest wiper contact point with rye was to be held at least 2 inches above the wheat. Residues in excess of 0.2 ppm in wheat grain are not anticipated.

2) Formulation to be used was Roundup® (Mon 2139). Inerts are cleared under 180.1001.

3) Toxicological Studies:

No new data were submitted.

A) Supportive toxicological data include many acute studies with the formulation demonstrating low oral and dermal toxicity and minimal ocular and dermal irritation (memo Sept. 18, 1981, W. Dykstra to R. Taylor).

Acute oral - rats — LD_{50} > 5,000 mg/kg (Same result with "W" or "AA" formulations)

Acute dermal - rabbit — LD_{50} > 5,000 mg/kg (Same result with "W" or "AA" formulations)

Eye irritation - rabbit - score = 19.6/110 unwashed "W" formulation

7.6/110 washed "W" formulation

20.1/110 unwashed "AA" formulation

7.3/110 washed "AA" formulation

All signs of irritation had disappeared in unwashed eyes by 10-14 days and by 7 days in washed eyes following instillation.

Dermal irritation - score = 0.5/8.0 "W" formulation
1.1/8.0 "AA" formulation

B) Teratology studies (memo of 2/3/81 from W. Dykstra to R. Taylor) include:

Rat teratology - negative at 3500 mg/kg/day
- severe maternal toxicity at 3500 mg/kg/day
- fetotoxic NOEL was 1000 mg/kg/day

Rabbit teratology - negative at 350 mg/kg/day
- fetotoxic NOEL was 175 mg/kg/day

C) Mutagenic studies include no evidence of mutagenicity in (memo of Alexander to P.M. #25 dated 9/22/79):

a) Rec-Assay in two strains of B. sublilis up to 2000 ug/test material/disk.

b) Reverse mutation in five histidine - requiring strains of S. typhimurium and one tryptophan - requiring strain of E. coli, with and without metabolic activation.

c) Ames test in four strains of Salmonella, with and without activation.

d) A dominant lethal study in the mouse (memo of W. Dykstra to R. Taylor dated 2/3/81) which was negative at 2000 mg/kg.

D) Oncogenic and Chronic Oral Toxicity: A 2-year chronic oral toxicity study in the dog has recently been evaluated and declared inadequate (memo of 7/27/82 from Teeters to Taylor). A 2-year chronic/oncogenic study in the rat (Bio/dynamics, 9/18/81) is acceptable; the NOEL is 31 mg/kg/day and the oncogenic potential is negative (memo of 4/8/82 from W. Dykstra to R. Taylor). Since the dog chronic toxicity study has been declared inadequate there is now a data gap for chronic toxicity in a non-rodent species.

E) A three-generation reproduction study in rats has a NOEL of 10 mg/kg/day based on pathological findings of renal focal tubular dilation in male F_{3b} weanlings (memo of 7/21/82 from Teeters to Taylor [25]).

F) A dermal patch study with humans using the use level (1:9 dilution of 30% water based chemical) and 5x the use level of MON 2139 showed that the test material was not a primary irritant, fatiguing agent nor a sensitizer (memo of 8/2/74 from R. Landolt on PP#5G1523).

G) Note on other IBT studies validated by Canada:

The following additional studies have been validated by the Canadian government and determined to be valid; they, therefore, remain as part of the data base for glyphosate. However, evaluations have not been performed on these studies and hence their utility in supporting the proposed use has not been ascertained at the present time.

IBT#B-1020 - 90-Day Oral - Rat

IBT#C-1021 - 90-Day Oral - Dog

IBT#8580-09117 - 42-Day Neurotoxicity - Chicken

IBT#B-566 - 3-Generation Reproduction - Rat (this study, although listed as valid in a Canadian Validation Summary dated March 1, 1982, was classified invalid in their validation report dated 4/8/81; this discrepancy should be resolved).

Therefore, the status of the subchronic oral in a non-rodent is not clear.

4) Several tolerances have been established under 40 CFR 180.364; the one for grains is 0.1 ppm.

5) Evaluation of the ADI.

Based on a NOEL of 10 mg/kg/day in the reproduction study and using a safety factor of 100, the ADI is 0.1 mg/kg/day (10 mg/kg/day x $\frac{1}{100}$ = 0.1 mg/kg/day).

The MPI for a 60 kg person is 6 mg/kg.

6) The published tolerances utilize 5.84% of the ADI. Total published and unpublished, but Tox approved, tolerances utilize 23.28% of the ADI. All tolerances, including the one in this action, utilize 23.80% of the ADI and the TMRC is 1.4282 mg/day based on a 1.5 kg diet. This current action permitting the use of glyphosate in certain wheat fields will utilize only 0.52% of the ADI.

7) No regulatory actions are pending against the pesticide and no RPAR criteria have been exceeded.

8) Other relevant considerations:

Concentrations of 0.1 - 0.13 ppm of N-nitrosoglyphosate (NNG) are present in the technical product (isopropylamine salt of glyphosate) and 0.2 - 0.4 ppm in the formulated product (Roundup®) (Memo of 12/2/77 from RCB, PP#7F1971/FAP 7H5168). It has been EPA's interim policy to routinely register (except in special cases) pesticides whose N-nitroso compound content is less than 1 ppm (Fed Reg. Vol. 5, No. 124, 6/25/80). No detectable residues of NNG were found in soybean grain, forage and hay or in cottonseed using an analytical method sensitive to 0.02 ppm. Similar results would be expected with this use on wheat, particularly since the herbicide is not applied

directly to the plant (personal conversation with R. Loranger, RCB). Additional data based on activity measurements from tracer studies with ^{14}C-glyphosate indicate maximum hypothetical residues of < 1-7 ppb NNG (Memo of 12/2/77 from RCB, PP#7F1971/FAP 7H5168). Such levels in wheat from a one-time use in a limited locate, as proposed by this action, are not of serious toxicological concern. Additionally, no detectable exposure to NNG by applicators or during re-entry was found for other crops (Toxicology Branch memo of 9/26/78; Accession No. 233914). However there are three unvalidated IBT studies with NNG which need to be validated and, if necessary, evaluated. These studies are:

IBT#8560-8924 - 2-year oral - rat

IBT#8580-8922 - 2-year oral - dog

IBT#8533-08923 - 3-generation reproduction - rat

Also, during a phone conversation on 8/9/82 with Dr. Duncan of Monsanto, he reported the existence of an oncogenic study in mice in which the sodium salt of NNG was administered by gavage; the in-life phase has been completed and the study will be reported in the first quarter of 1983.

9) Conclusion:

The crisis exemption for the use of glyphosate on wheat in the state of Oregon can be toxicologically supported.

Chronic oral toxicity data in a non-rodent species is a data gap, and the status of subchronic data in a non-rodent is unclear.

WRD for LPC 8/20/82

Winnie Teeters

Winnie Teeters, Pharmacologist
Toxicology Branch
Hazard Evaluation Division (TS-769)

8/20/82

TS-769:th:TOX/HED:WTeeters:8-18-82:card 2

CFR 180.364 Glyphosate Roundup 7/19/82

File last updated 7/19/82

NOEL change not needed per

ACCEPTABLE DAILY INTAKE DATA

RAT, Older	NOEL	S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	mg/day(60kg)
10.000	200.00	100	0.1000	6.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Grain Crops(64)	0.100	13.79	0.2069
Avocados(6)	0.200	0.03	0.00009
Citrus Fruits(33)	0.200	3.81	0.01144
Coffee(36)	1.000	0.75	0.01119
Grapes, inc raisins(66)	0.100	0.49	0.00074
Leafy Vegetables(80)	0.200	2.76	0.0828
Nuts(101)	0.200	0.10	0.00031
Pome Fruits(126)	0.200	2.79	0.0837
Root Crop Veg(138)	0.200	11.00	0.03299
Seed&Pod-Veg(143)	0.200	3.66	0.01098
Soybeans (oil)(148)	6.000	0.92	0.06263
Palm Oil(202)	0.100	0.03	0.00005
Pistachio-nuts(210)	0.100	0.03	0.00009
Asparagus(5)	0.200	0.14	0.0043
Bananas(7)	0.200	1.42	0.00426
Olives(104)	0.100	0.06	0.00009
Stone Fruits(151)	0.200	1.25	0.00374
Sugar,cane&beet(154)	2.000	3.64	0.10915
Molasses(96)	20.000	0.03	0.00920
Cranberries(44)	0.200	0.03	0.00009
Cottonseed (oil)(41)	15.000	0.15	0.03375
Kidney(203)	0.500	0.03	0.00023
Liver(211)	0.500	0.03	0.00023
Peanuts(115)	0.100	0.36	0.00054
Guava(184)	0.200	0.03	0.00009
Papayas(109)	0.200	0.03	0.00009
Mangoes(66)	0.200	0.03	0.00009

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	0.3498 mg/day(1.5kg)	~~5.83~~ 5.84

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Unpublished,Tox Approved 9F2163,2329,1E2444,1G2440,2F2634,9H5204,1H53

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cucurbits(49)	0.100	2.84	0.00426
Fruiting Vegetables(60)	0.100	2.99	0.00449
Small Fruit,berries(146)	0.100	0.83	0.00124
Hops(73)	0.100	0.03	0.00005
Fish,shellfish(59)	2.000	1.08	0.03250
Potable Water(198)	0.500	133.33	1.00000
Pineapple(123)	0.100	0.30	0.00044
Tea(162)	4.000	0.07	0.00429

June 2,

MPI	TMRC	% ADI
		23.28

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Current Action Section 18

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Wheat(170)	0.200	10.36	0.03109

MPI	THRC	% ADI
6.0000 mg/day(60kg)	1.4282 mg/day(1.5kg)	23.80

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