OK

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

SEP 3 1982

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor (25)
Registration Division (TS-769)

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

John W. Melone, Acting Director
Hazard Evaluation Division (TS-769)

SUBJECT: Glyphosate (Roundup®), Increase temporary tolerances in/on soybean grain and soybean hulls, PP#2G2686; PP#2H5363; Reg No. 524-308 CASWELL#661A

Recommendations:

1. This request to increase temporary tolerances for glyphosate in/on soybean grain and hulls can be toxicologically supported.

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

3. Data should be provided showing the residue of glyphosate in soybean oil when soybeans have a residue of 10 ppm.

Review:

1. Requested Actions

This petition requests that a temporary tolerance be established for the combined residues of the herbicide N-phosphonomethyl glycine (glyphosate) and its metabolite, aminomethylphosphonic acid, in or on the raw agricultural commodity as follows:

Soybean grain -------- 10.0 ppm

A food additive tolerance for soybean hulls proposed as follows:

Soybean hulls -------- 30.0 ppm

A need for the increased tolerances is due to application of glyphosate as a preharvest topical treatment for weed control in soybeans.

The EUP program will involve research trials in 27 major soybean producing states. Average size of the plots will be 5 acres and rates of application up to 4.5 lbs acid equivalent (a.e.) per acre will be used. When the program is completed approximately 2,880 lb a.e. of the glyphosate will have been applied to 1,920 acres in each of 2 years.

2. The formulation to be used will be Roundup® (MON 2139). Inerts are cleared under 180.1001.

3. Toxicological Studies:

No new data were submitted.

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

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

Acute dermal - rabbit - LD_{50} > 5,000 mg/kg (same results with "W" or "AA" formulation)

Eye irritation - rabbit - Scores - 19.6/110 unwashed "W" formulation

7.6/100 washed "W" formulation

20.1/110 unwashed "AA" formulation

7.3/110 washed "AA" formulation

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

Dermal irritation - rabbit - Scores - 0.5/8.0 "W" formulation
1.1/8.0 "AA" formulation

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

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

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 metabolic activation.

d) A dominant lethal study in the mouse (memo of 2/3/81 from W. Dykstra to R. Taylor) 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.

Another data gap is an oncogenic study in a second 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 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; a similar commodity, palm oil, has a tolerance of 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 ($10 \text{ mg/kg/day} \times \frac{1}{100} = 0.1 \text{ mg/kg/day}$).

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

Estimated Total Glyphosate Intake for Infants

The estimated total glyphosate intake for infants 0-3 months of age will be 0.144 mg/kg/day for milk-based and 0.197 mg/kg/day for soy-based formulas, which will utilize 144 and 197%, respectively, of the ADI.

Calculation of the estimated glyphosate intake for infants had to consider these actions pertaining to coconuts as well as pending ones (PP#2G2686 & PP#2H5363) for use of glyphosate in/on soybean grain and hulls and recently approved ones (PP#9F2163, 9H5204) for use on or around aquatic sites,which included a

level in potable water. Both soybean oil and coconut oil are used in the preparation of infant formula and the highest water content of three such commercially available formulas (Enfamil® Similac® and Advance Nutritional Beverage®) was found to be in Enfamil®, which is diluted 1:1 with water for use and contains 90.4% water in the can (resulting in approx. 95% water as prepared for use).

Equations for estimating pesticide content of milk-based and soy-based infant formulas were taken from a Chaisson et al paper in preparation (An Exchange Model for Estimating Infant's Total Dietary Exposure to Pesticides, Chaisson, C.F., Peterson, B.J., Rathman, S.S. and White, S.B., in preparation). In calculations of the estimated total glyphosate intake for infants, "worst case" conditions were considered when definitive information was available, such as the fact that for glyphosate the highest exposure occurs for infants 0-3 months old who consume formula almost totally exclusive of other foods; exposure is highest for this age group since tolerances are non-existent or very low for glyphosate in fruits, vegetables and meats which contribute to diets of older infants who consume proportionately less formula and eat more solid foods. The same policy of using "worst case" conditions was utilized when definitive information was missing; for instance, the total tolerance for soybeans was used because distribution in soybean oil from a residue of 10 ppm on soybeans was not available (although it is known that glyphosate does not concentrate in the oil; see below).

Both of the estimated glyphosate intake values for infants 0-3 months old exceed the ADI of 0.1 mg/kg/day, but several factors in "real life" will mitigate against the worst case conditions considered in the calculations.

The contribution alone of the level of glyphosate in potable water (0.5 ppm) for this age group of infants exceeds the ADI, being 0.104 mg/kg/day; but realization of such an exposure is remote. The level in water is based upon "raw water" yet most potable water will have been processed in some manner (thereby probably reducing the level) by municipalities, and this is more particularly the case for water used in manufacture and home preparation of formula for infants. Moreover, the level in water is based on time zero values and levels will decrease rapidly and substantially thereafter. Additionally, glyphosate treatment of aquatic sites will be made, at the most, only twice yearly. Consequently, the water in a 3-month-old infant's formula would, in all probably, be exposed to only one such treatment and unless the water were taken immediately at time zero at the place of treatment a level of 0.5 ppm would not be attained.

The tolerance for the raw agricultural commodity soybeans was used for calculating the contribution of glyphosate in soybean oil to infants' diet since the level in oil from the tolerance requested on soybeans was not available. However data are available showing that glyphosate does not concentrate in the oil; soybeans with total residues of 2.3 ppm produced residues of 6.0 ppm in hulls (3x conc.) 2.0 ppm in the meal and nondetectable (<0.05 ppm) in the oil (Memo of June 17, 1982 from Propst to Taylor on PP#2G2686). Actual levels in oil from residues of 10 ppm on soybeans will be requested.

Although the estimated glyphosate intake for "worst case" situations for very young infants exceeds the ADI, several reasons are presented which are expected to moderate such worst case conditions resulting in a lower intake.

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 ones in this action, utilize 23.29% of the ADI and the TMRC is 1.3972 mg/day based on a 1.5 kg diet.

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.

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 coconut and copra (food factors of 0.03 each) 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:

a) This request to establish permanent tolerances for copra and associated coconut products can be toxicologically supported.

b) Chronic oral toxicity data in a non-rodent species and an oncogenic study in a second species are data gaps, and the status of subchronic data in a non-rodent is unclear.

Winnie Teeters

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TS-769:TOX/HED:th:WTeeters:8-26-82:card 2

NOEL change not recorded per

CFR 180.364 Glyphosate [illegible] 7/22/82

File last updated 7/22/82

ACCEPTABLE DAILY INTAKE DATA

Rat, Chronic NOEL mg/kg	ppm	SF	ADI mg/kg/day	MPI mg/day(60kg)
10.000	200.0	100	0.1000	6.0000

Published Tolerances

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Grain Crops(64)	0.100	13.7[illegible]	[illegible]2069
Avocados(5)	[illegible]	0.03	[illegible]
Citrus Fruits(33)	0.2[illegible]	3.[illegible]1	[illegible]0111[illegible]
Coffee(36)	1.000	0.7[illegible]	[illegible]0111[illegible]
Grapes, inc raisins([illegible])	0.100	0.[illegible]5	[illegible]7[illegible]
Leafy vegetables([illegible])	[illegible]	[illegible].70	[illegible]02[illegible]
Nuts(1[illegible])	[illegible]	[illegible]	[illegible]031
Pome Fruits(1[illegible])	[illegible]	2.7[illegible]	0.00[illegible]37
Root Crop Veg(1[illegible])	[illegible]	11.[illegible]	[illegible]
Seed&Pod Veg(1[illegible])	[illegible]	3.[illegible]	[illegible]
Palm Oil([illegible])	[illegible]	0.[illegible]3	[illegible]
Pistachio Nuts([illegible])	[illegible]	0.03	[illegible]
Asparagus([illegible])	[illegible]	[illegible]	[illegible]
Bananas(7)	[illegible]	1.[illegible]	[illegible]
Olives(1[illegible])	[illegible]	0.[illegible]	[illegible]
Stone Fruits(1[illegible])	[illegible]	1.2[illegible]	[illegible]0374
Sugar,Cane&Beet(1[illegible])	2[illegible]	3.[illegible]	[illegible]10515
Molasses([illegible])	20.000	0.03	[illegible]0
Cranberries([illegible])	[illegible]	0.03	[illegible]
Cottonseed (oil)([illegible])	1[illegible]	[illegible]	[illegible]373
Kidney(2[illegible])	[illegible]	0.03	[illegible]
Liver(211)	[illegible]	0.03	[illegible]
Peanuts(11[illegible])	[illegible]	0.30	[illegible]
Guava(1[illegible])	[illegible]	0.[illegible]	[illegible]
Papayas(1[illegible])	[illegible]	0.[illegible]3	0.[illegible]
Mangoes([illegible])	[illegible]	0.03	0.[illegible]
Soy. Bean (oil) (1[illegible])	[illegible]	[illegible]	[illegible]

TMRC		% ADI
[illegible] mg/day(1.5kg)	[illegible]34[illegible] mg/day(1.5kg)	[illegible]

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Unpublished, Tox Approved [illegible]2103,2529,[illegible],[illegible],[illegible],[illegible],1.[illegible]

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Cucurbits([illegible])	[illegible]	2.[illegible]	[illegible]
Fruiting Vegetables([illegible])	0.100	[illegible]	[illegible]
Small Fruit,Berries(1[illegible])	[illegible]	[illegible]	0.[illegible]
Figs(7[illegible])	[illegible]	0.03	0.[illegible]
Fish,Shellfish([illegible])	[illegible]	1.[illegible]	0.[illegible]
Potable Water(1[illegible])	0.[illegible]	133.33	1.[illegible]
Pineapple(1[illegible])	[illegible]	0.30	[illegible]
[illegible](1[illegible])	4.000	[illegible]7	[illegible]429

[illegible]

TMRC		% ADI
[illegible]	1.3971 mg/day(1.5kg)	23.26

Current regs ...00/2H5365

Class	Tolerance food factor, mg/day(1.5kg)
soybeans (oil)(1.5)	[illegible] 0.02 0.03000

.01	1.00	4 fl
0.0000 mg/day(1kg)	1.0000 mg/day(1.5kg)	2[illegible].00