Glyphosate/Tox

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

releasable

SEP 30 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#3E2929; Glyphosate in/on acerola, figs, kiwifruit, and olives. Accession # 071750.

Caswell # 661A

TO: Hoyt Jamerson
Product Manager No. 43
Registration Division (TS-767)

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Christine F. Chaisson, Ph.D. F Chaisson 9/24/83
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

Recommendations:

1. The proposed tolerances are not toxicologically supported.

2. The following study is required to be submitted to support the proposed tolerances.

   a. Mouse oncogenicity study.

3. A chronic oral dog study is required to be submitted within a reasonable period of time.

Review

1. Section F

PROPOSED TOLERANCE FOR THE PESTICIDE CHEMICAL GLYPHOSATE IN OR ON ACEROLA, KIWIFRUIT, FIGS, AND OLIVES

The petitioner, IR-4 National Director, Dr. R. H. Kupelian, on behalf of the IR-4 Technical Committee and

the Agricultural Experiment Stations of California and Puerto Rico requests the establishment of a tolerance for the combined residues of glyphosate (N-(phosphonomethyl)glycine) and its metabolite aminomethylphosphonic acid in or on the raw agricultural commodities acerola, figs, kiwifruit, and olives at 0.2 ppm.

2. No new toxicity data were submitted.

3. The formulation to be used is Roundup (EPA Reg. No. 524-308-AA; inerts are cleared under Section 180.1001).

4. Toxicological data considered for the tolerances:

   - o Teratology - rat - negative at 3500 mg/kg/day; fetotoxic NOEL was 1000 mg/kg/day
   - o Teratology - rabbit - negative at 350 mg/kg/day; fetotoxic NOEL was 175 mg/kg/day
   - o Mutagenicity - negative in the following studies:
     - a. Rec-assay in two strains of B. subtilis up to 2000 ug/test.
     - b. Reverse Mutation in 5 histidine - requiring strains of S. typhimurium and 1 tryptophan-requiring strain E. coli, with and without metabolic activation.
     - c. Ames test in four strains of Salmonella, with and without metabolic activation.
     - d. Dominant lethal study in the mouse at 2000 mg/kg.
   - o Three-generation reproduction - rat - NOEL of 10 mg/kg/day based on pathological findings of renal focal tubular dilation in high dose male F_{3b} weanlings.
   - o Chronic/oncogenic - rat - NOEL was 31 mg/kg/day; oncogenic potential was negative.

Recently (memo dated 2/20/83 from Dykstra to Taylor), a question has arisen concerning the significance of the incidence of C-cell carcinomas of the thyroid in female rats in the life-time feeding study in this species with Glyphosate, and the thyroid slides will be reevaluated; the tentative conclusion reached is that Glyphosate was not oncogenic in that study. A final conclusion that Glyphosate is not oncogenic in that study has been presented in PP#3E2845, memo of 4/5/83 by Dr. L. Kasza based on re-evaluation of slides by Dr. Capen.

5. Data considered desirable but lacking are a mouse oncogenicity study and a chronic oral dog study.

6. Tolerances are established under 40 CFR 180.364. No regulatory actions are pending against the pesticide and no RPAR criteria have been exceeded.

7. The following considerations are relevant:

A two-year oral dog study (No. 651-00565) done at IBT has recently (7/27/83) been evaluated and declared invalid. 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 perfortmed on these studies and hence their utility in supporting the proposed use has not been ascertained at the present time.

IBT No. B-1020 - 90-Day Oral - Rat

IBT No. C-1021 - 90-Day Oral - Dog

IBT No. 8580-09117 - 42-Day Neurotoxicity - Chicken

IBT No. 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 April 8, 1981; this discrepancy should be resolved).

Furthermore, 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 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 No. 8560-8924 - 2-year oral - rat

IBT No. 8580-8922 - 2-year oral - dog

IBT No. 8522-08923 - 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.

8. Evaluation of the ADI:

Based on a NOEL of 10 mg/kg/day in the reproduction study (Bio/dynamics, 9/18/81) and using a safety factor of 100, the ADI is 0.1 mg/kg/day (10 mg/kg $\times \frac{1}{100}$ = 0.1 mg/kg/day).

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

9. Published tolerances utilize 22.74% of the ADI. Tox approved unpublished tolerances utilize the ADI to 23.73%. The current action utilizes 0.01% of the ADI.

William Dykstra

William Dykstra, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

DCR-32894:Stoutamire/Dykstra:TOX - 39:CM#2:Rm803:557-7560:9/19/83:efs
REVISED:09/22/83:DCR-10753:pad

CFR 180.364 Glyphosate Roundup 9/1/83

File last updated 3/16/83

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI 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	0.02069
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	0.00828
Nuts(101)	0.200	0.10	0.00031
Pome Fruits(126)	0.200	2.79	0.00837
Root Crop Veg(138)	0.200	11.00	0.03299
Seed&Pod Veg(143)	0.200	3.66	0.01098
Palm Oil(202)	0.100	0.03	0.00005
Pistachio nuts(210)	0.200	0.03	0.00009
Asparagus(5)	0.200	0.14	0.00043
Bananas(7)	0.200	1.42	0.00426
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(88)	0.200	0.03	0.00009
Soybeans (oil)(148)	6.000	0.92	0.08263
Pineapple(123)	0.100	0.30	0.00044
Fish,shellfish(59)	0.250	1.08	0.00406
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
Potable Water(198)	0.500	133.33	1.00000
Olives(104)	0.100	0.06	0.00009

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.3643 mg/day(1.5kg)	22.74

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Unpublisned,Tox Approved 2F2680,2G2686,1H5310

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	4.000	0.92	0.05509
Tea(162)	4.000	0.07	0.00429
Coconut(35)	0.100	0.03	0.00005

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.4238 mg/day(1.5kg)	23.73

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Current Action 3E2929

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Acerola (214)	0.200	0.03	0.00009
Figs(57)	0.200	0.03	0.00009
Kiwi Fruit(204)	0.200	0.03	0.00009
Olives(104)	0.100	0.06	0.00009

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.4241 mg/day(1.5kg)	23.74

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