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

MEMORANDUM AUG 11 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
Registration Division (TS-767).

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

SUBJECT: "Eight Point Summary" for Glyphosate (Roundup®) tolerance on tea, PP#1H5310, EPA Reg.#524-308 CASWELL#661A

Petitioner: Monsanto Company
1101 17 Street, N.W.
Washington, D.C. 20036

Per your request, the following 8 point summary is provided.

1. Data considered in setting the tolerance:

A) Teratology - rat - negative at 3500 mg/kg/day; fetotoxic NOEL was 1000 mg/kg/day

Teratology - rabbit - negative at 350 mg/kg/day; fetotoxic NOEL was 175 mg/kg/day

B) 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 of 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

C) 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.

D) Chronic/oncogenic - rat - NOEL was 31 mg/kg/day; oncogenic potential was negative.

2. Data considered lacking but desirable:

   a. Chronic oral toxicity in a non-rodent species

   b. Oncogenic study in a second species

3. Actions being taken to obtain lacking but desirable data:

   Oncogenic study in mice is underway. On 8/9/82 Dr. Duncan reported by phone that a rat 90-day oral study at levels up to 6000 ppm is to be submitted to the Agency next month.

4. Other tolerances granted: See attached printout.

5. Effect of tolerance on the ADI:

   Published tolerances utilizes 5.84% of the ADI. Total published and unpublished, but Tox approved, tolerances utilize 23.21% of the ADI. All tolerances, including the one in this action, utilize 23.28% of the ADI and the TMRC is 1.3971 mg/kg based on a 1.5 kg diet. This current action permitting the use of Glyphosate on tea will utilize 0.07% of the ADI.

6. Basis for ADI:

   The ADI is based on a NOEL of 10 mg/kg/day in the rat reproduction study. Using this value and 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).

   For a 60 kg person the MPI is 6 mg/day.

7. Pending regulatory actions against registration: NONE

8. Other relevant considerations:

A two-year oral dog study (No. 651-00565) done at IBT has recently (7/27/82) been evaluated and declared invalid (see attached memo). 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).

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. Similar results would be expected with this use on tea, 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 tea (food factor of 0.07) 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

3

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.

Attachment

doc 3/11/82

Winnie Teeters

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

TS-769:th:TOX/HEDWTeeters:8-6-82:card 2

...ed Tolerance Approach ...roup 6/6/32

Unverified Printout not recorded

...Chronic Daily Intake Data

Total Diet Mode		Sex	ADI	MPI
mg/kg	Sex		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	13.75	0.02063
Avocados(6)	0.200	0.05	0.00007
Citrus Fruits(33)	0.200	3.21	0.01144
Coffee(36)	1.000	0.75	0.01119
Grapes, inc raisins(38)	0.100	0.49	0.00074
Leafy Vegetables(60)	0.200	2.76	0.00828
Nuts(101)	0.200	0.10	0.00031
Pome Fruits(120)	0.200	2.79	0.00837
Root Crop Veg(130)	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)	0.100	0.14	0.00043
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,canesbeet(154)	2.000	3.64	0.10915
...classes(96)	20.000	0.03	0.00020
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	0.0023
Peanuts(115)	0.100	0.36	0.0054
Guava(134)	0.200	0.03	0.00009
Papayas(139)	0.200	0.03	0.00009
...anges(66)	0.100	0.03	0.0009
Soybeans (oil)(146)	6.000	0.92	0.08263

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	0.3496 mg/day(1.5kg)	5.83 5.84

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Unpublished,Tox Approved 3F2163,2329,1B2444,1B2440,2F2334,9H5204,2826

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cucurbits(49)	0.100	2.84	0.00427
Fruiting Vegetables(60)	0.200	2.99	0.00449
Small Fruit,Berries(140)	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(196)	0.500	133.33	2.00000
Pineapple(123)	0.100	0.30	0.00045

(5)

Also publish

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.3926 mg/day(1.5kg)	23.21