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

SUBJECT: Glyphosate (Roundup®) tolerances on or around aquatic sites - PP#9F2163; PP#9H5204, EPA Reg.#524-308, CASWELL#661A

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

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. Dr. Duncan of Monsanto reported by phone on 8/9/82 that there was a 90-day rat oral study up to 6000 ppm to be submitted to the Agency next month.

4. Other tolerances granted: See attached printout,

5. Effect of tolerances on the ADI:

Published tolerances utilize 5.84% of the ADI. The tolerances proposed in this action utilize 17.38% of the ADI and the TMRC is 1.0425 mg/day based on a 1.5 kg diet. Published and unpublished tolerances utilize 23.28% of the ADI.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, N-nitrosoglyphosate (NNG) residues in flowing waters treated with glyphosate were reported at levels less than 2 ppb (RCB memo of 11/23/81 on PP#9F2163/ FAP#9H5204). It is not clear whether these were actual analytical values or the limit of the level of method sensitivity; this question is referred to RCB for resolution. Considering the low level of NNG residues in water, it may be that this is not of serious toxicological concern. 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

Additionally, in a phone conversation between Dr. Duncan and L. Chitlik on 8/9/82 it was learned that an eighteen-month oncogenic study in hamsters with NNG done at Bio/dynamics was terminated at 12 months due to high mortality in all groups, including controls; the highest level used was 30 mg/kg and no compound related effects were reported by Dr. Duncan. The report of this study was requested by R. Engler in his memo of August 30, 1978.

The in-life portion of an oncogenic study in mice in which the sodium salt of NNG was administered by gavage has been completed and pathological evaluation is in progress. This study will be reported in the first quarter of 1983 according to Dr. Duncan.

Attachments

FDC 8/11/82

Winnie Teeters

Winnie Teeters, Pharmacologist
Toxicology Branch
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