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

FEB 5 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTA

MEMORANDUM

SUBJECT: PP#1E2444;-Glyphosate in or on Papaya at 0.2 ppm
CASWELL#661A; Accession#099751

FROM: William Dykstra, Toxicologist
Toxicology Branch, HED (TS-769)

iWYD FDC 1/26/81

TO: Clint Fletcher (43)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

WDB

Recommendations:

1) The requested tolerance can be toxicologically supported.

2) The following studies are currently lacking and are required to be submitted within a reasonable period of time:

a) oncogenicity - 2 species

Section F

The petitioner, IR-4 National Director, Dr. R.H. Kupelian, on behalf of the IR-4 Technical Committee and the Agricultural Experiment Station of Hawaii requests the establishment of a tolerance for combined residues of Glyphosate and its metabolite, aminomethylphosphonic acid, resulting from herbicide applications of the isopropylamine salt of Glyphosate in or on the raw agricultural commodity papaya at 0.2 ppm.

A. Formulation to be used is Roundup (EPA Reg.#524-308). Inerts are cleared under 180.1001.

Review:

1) Memo of 8/22/78 from R. Engler to R. Taylor. Toxicology Branch has reviewed the validated studies in support of Glyphosate.

a) Data considered

- Oral LD_{50} Rabbit: 3.8 gm/kg (valid)
- 90-Day Rat Feeding: NOEL = 2000 ppm (valid)
- 90-Day Dog Feeding: NOEL = 2000 ppm (valid)
- Teratology (2 studies) Rabbit: Negative at 30 mg/kg/day (highest dose); repeat studies with a higher dose.
- 2-Year Dog Feeding: NOEL = 300 ppm (valid)
- 3-Generation Rat Reproduction: NOEL = 100 ppm (valid)
- 18-Month Mouse Feeding: No carcinogenic potential at 300 ppm (highest dose). Study must be repeated since too many animals are missing.
- 2-Year Rat Feeding: NOEL = 100 ppm (valid) Study is adeqaute to determine the toxic effects, but only marginal with respect to oncogenic evaluation since too few animals examined. As reported the study shows no oncogenic potential.
- Neurotoxicity (hen): Negative at 7.5 gm/kg (cumulative for 3 days) (valid)
- Dominant Lethal (mice): Negative at 10 mg/kg (highest dose), supplemental study, no records of positive control.
- Host-Mediated Assay: Negative (valid)
- Ames-Assay: Negative (supplemental study) no raw data available.
- Rec-Assay: Negative (supplemental study) no raw data available.

2. Memo of 9/22/79 from M.L. Alexander to Product Manager #25. Glyphosate was not mutagenic in the following test systems:

a) Rec-assay in two strains of B. subtilis 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 or without metabolic activation.

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

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3) Memo of 1/16/81 from W. Dykstra to R. Taylor.

a) Rat Teratology: Severe maternal toxicity at 3500 mg/kg/day;
Negative at 3500 mg/kg/day
Fetotoxic NOEL = 1000 mg/kg/day

b) Rabbit Teratology: Negative at 350 mg/kg/day
Fetotoxic NOEL = 175 mg/kg/day

c) Mouse Dominant Lethal: Negative at 2000 mg/kg

4) No new toxicity data were submitted with this petition.

5) Evaluation of the ADI

The ADI is based on the NOEL of 100 ppm (5 mg/kg/day) in a 2-year rat feeding study. This is the most sensitive species for which chronic toxicity data are available. A 100 fold safety factor was used to calculate the ADI.

$$ADI = NOEL \times \frac{1}{100}$$

$$ADI = 5 \text{ mg/kg/day} \times \frac{1}{100} = 0.05 \text{ mg/kg/day}$$

The MPI for a 60 kg person is 3 mg/day

6) Tolerances have been established under 40 CFR 180.364.

7) No regulatory actions are pending against the pesticide.

8) The published tolerances utilize 7.21% of the ADI. Unpublished, Tox approved tolerances utilize the ADI to 20.18%. The current action does not utilizes any of the ADI. The TMRC is 0.00009 mg/day/1.5 kg. All tolerance on Glyphosate utilize 20.18% of the ADI. (computer printout attached).

Conclusions and Recommendations:

The requested tolerance can be toxicologically supported.

The oncogenic potential of Glyphosate is not fully elucidated. The chronic rat and mouse feeding studies, however, provide assurance that Glyphosate has a relatively low oncogenic potential. A further assurance of low risk with Glyphosate is found in the fact that on a theoretical basis the exposure via the diet is about one-fifth of the ADI at present.

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