Glyphosate / Tox

Caswell file 38

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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Releasable

MEMORANDUM

SUBEJCT: PP# 3E2893 Glyphosate in/on fruiting vegetables; Revised Section F; Addendum to risk assessment
Caswell #: 661A

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: Hoyt Jamerson
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and

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Hazard Evaluation Division (TS-769)

THRU: Robert P. Zendzian, Ph.D. 3/5/85
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 3/26/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

Requested Action:

Review request for permanent tolerances for glyphosate in/on fruiting vegetables.

Background:

Glyphosate has been identified as an oncogen in male mice. A dose-related increase in renal tubule adenomas was found. These tumors are considered compound-related.

A consensus review of these findings is attached.

A Toxicology Branch review of the mouse study will be forthcoming.

The Q^* value for glyphosate is 5.9×10^{-5} $(mg/kg/day)^{-1}$ based on the incidence in mice of renal tubule adenomas.

Recommendations:

1. The oncogenic risk for published tolerances is 1.4×10^{-6}. The oncogenic risk for the current action is 4.4×10^{-9}. Additionally, the percent increase in the TMRC is 0.3%.

2. Toxicology Branch makes no conclusions regarding the acceptability of oncogenic risks.

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

Review:

Section F: Proposed Tolerance for the Pesticide Chemical Glyphosate in or on Fruiting Vegetables.

Pesticide Petition No. 3E2893.

The petitioner, IR-4 National Director, Dr. R.H. Kupelian, on behalf of the IR-4 Technical Committee and the Agricultural experiment Stations of Arkansas, California, Florida, Louisiana, Maryland, Michigan, Tennessee, New Jersey, New York, North Carolina, Oregon, Puerto Rico, South Carolina, Texas, Kentucky, Virginia, Washington, and the U.S. Department of Agriculture requests the establishement of a tolerance for the residues of glyphosate (N-phosphonomethyl)glycine) and its metabolite aminomethylphosphonic acid resulting from the application of the isopropylamine salt of glyphosate in or on the raw agricultural commodity group fruiting vegetables (except cucurbits), including tomatoes, peppers and egglants at 0.1 ppm.

2. No new toxicity data were submitted.

3. The formulation to be used in 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. 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 oncogneic in that study has been presented in PP#3E2845, memo of 4/5/83 by Dr. L. Kasza.

5. Data considered desirable but lacking is a chronic oral dog study.

6. Tolerances are established under 40 CFR 180.364. No regulatory actions are pending against the pesticide.

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 performed 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 form 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. Calculation of oncogenic risk from published tolerances and the present action.

a. The TMRC for published and approved tolerances is 1.4238 mg/day/1.5 kg. This level is 2.4×10^{-2} mg/kg/day.

The oncogenic risk for published tolerances is as follows:

Risk = dietary exposure X Q^*
Risk = 2.4×10^{-2} mg/kg/day
X 5.9×10^{-5}/mg/kg/day)$^{-1}$; Risk = 1.4×10^{-6}.

b. The TMRC for the current action is 0.00449 mg/day/1.5 kg. This level is $7.5\ 10^{-5}$ mg/kg/day. The oncogenic risk for the current action is as follows:

Risk = dietary exposure X Q^*
Risk = 7.5×10^{-5} mg/kg/day
X 5.9×10^{-5} (mg/kg/day)$^{-1}$ Risk = 4.4×10^{-9}.

9. Evaluation of the ADI: Although glyphosate is oncogenic and will be regulated by a risk assessment, an ADI calculation has been used to assess systemic toxicity due to other effects (reproductive). 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 X $\frac{1}{100}$ = 0.10 mg/kg/day).

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

10. Published tolerance utilize 22.81% of the ADI. TOX approved, unpublished tolerances utilize the ADI to 23.7%. The current action utilizes 0.007% of the ADI. The increase in the TMRC is 0.00449 mg/day and results in and incremental percent increase of 0.3%.