Caswell file
(36)

Glyphosate / Tox

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Glyphosate; EPA Reg. #: 524-343; PP#3F2956; Glyphosate in/on shellfish; Addendum to risk assessment
Caswell #661A

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Robert P. Zendzian, Ph.D. 3/26/85
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

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

Requested Action:

Application to establish a residue tolerance for glyphosate in shellfish, and to register applications on tidewater areas and flooded rice levees.

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 $5.9 \times 10^{-5}(mg/kg/day)^{-1}$.

Recommendations:

1. The oncogenic risk for published tolerances is 1.4×10^{-6}. The oncogenic risk of the current action is 3.9×10^{-9}.

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

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

Review:

1. Proposed Residue Tolerance

glyphosate

40 CFR 180.364

Shellfish (molluscs & crustaceans)	0.25 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 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 are 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 is to be reported in the first quarter of 1983.

8. Calculation of oncogenic risk from published tolerances and the current 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 from 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 0.00406 mg/day/1.5 kg. This level is $6.7 \times ^{-5}$ mg/kg/day. The oncogenic risk for the current action is Risk = 6.7×10^{-5} mg/kg/day X 5.9 X 10-5 (mg/kg/day)-1 Risk = 3.9 X 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).

10. The MPI for a 60 kg person is 6 mg/day. Published tolerance utilize 22.81% of the ADI. TOX approved, unpublished tolerances utilize the ADI to 23.73%. The current action utilizes 0.006% of the ADI.