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

SEP 18 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 1, 1981

SUBJECT: EPA Reg.#524-308; Glyphosate; PP#9F2163; PP#9H5204; Additional information to support petitions requesting establishment of tolerances for Glyphosate and its metabolite on or around aquatic sites. CASWELL#661A Accession#070170

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

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

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Recommendations:

1. The requested tolerances and label amendments are not toxicologically supported. At least one new oncogenicity study must be submitted to support the significant increase in the TMRC due to the tolerance of 0.5 ppm in potable water.

2. Refer also to memo of 11/7/79 from W. Dykstra to R. Mountfort.

3. The submitted toxicology studies are acceptable as Core-Minimum Data and support the registration of the three Roundup formulations.

4. Oncogenicity studies in two species are required.

Review:

1. Revised Section F - Proposed Tolerances

A food additive tolerance of 0.5 ppm for potable water is requested for the combined residues of the herbicide glyphosate (N-phosphonomethyl-glycine) and its metabolite aminomethylphosphonic acid that result from applications on or around aquatic sites.

A residue tolerance of 0.2 ppm for fish is also requested.

Residue tolerances of 0.1 ppm are also requested in or on the following crop groupings: citrus, cucurbits, forage grasses, forage legumes, fruiting vegetables, grain crops, leafy vegetables, nut crops, pome fruits, root crop vegetables, seed and pod vegetables, small fruits, stone fruits and the individual crops: cottonseed, hops and avocados. Where tolerances are presently established at higher levels from other uses of glyphosate on the subject crops, the higher tolerance level should also apply to residues resulting from this use.

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

3. 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 (higher dose); repeat studies with 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 adequate 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 (supplemental study) no raw data available.
   - Rec-Assay: Negative (supplemental study) no raw data available.

4. 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.

5. 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
   Fetotoxicity NOEL = 1000 mg/kg/day

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

6. Toxicity Data Submitted with this Petition.

   A. Review of Mammalian Acute Toxicology Studies Included in this Submission

      a. Mammalian Acute Studies with MON 2139-NF80-W, Lot XLA-78, ML-80-362 (Monsanto, 6/3/81)

         1. Acute Oral Toxicity to Rats

            When the undiluted product was administered by stomach tube to fasted albino rats of both sexes, the acute oral LD_{50} was found to be greater than 5000 milligrams per kilogram body weight.

            Classification: Core-Minimum Data

         2. Acute Dermal Toxicity to Rabbits

            When undiluted material was held in continous 24-hour contact with abraded skin of albino rabbits of both sexes, the acute dermal LD_{50} was found to be greater than 5000 milligrams per kilogram body weight.

            Classification: Core-Minimum Data

3. Eye Irritation to Rabbits

When an 0.1 milliliter volume of undiluted formulation was instilled into the conjunctival sac of the rabbit eye, a moderate degree of irritation resulted. The average score on a scale of 110 of the 24-, 48-, and 72-hour readings was 19.6 for unwashed eyes and 7.6 for washed eyes. All signs of irritation had subsided in the unwashed eyes and washed eyes at 10 and 7 days after compound administration, respectively.

Classification: Core-Minimum Data

Primary Skin Irritation,

Essentially no irritation resulted after 0.5 milliliter of undiluted product was held in continuous 24-hour contact with intact and abraded rabbit skin. The Primary Irritation Index was 0.5 on a scale of 8.0.

Classification: Core-Minimum Data

Based on these test results MON 2139 NF80W would be classified as follows:

Oral toxicity - Category IV
Dermal toxicity - Category III
Eye irritation - Category II
Skin Irritation - Category IV

b. Mammalian Acute Studies with MON 2139-NF80-AA, Lot XLA-172, ML-80-366. (Monsanto, 6/3/81)

1. Acute Oral Toxicity to Rats

When the undiluted product was administered by stomach tube to fasted albino rats of both sexes, the acute oral LD_{50} was found to be greater than 5000 milligrams per kilograms body weight.

Classification: Core-Minimum Data

2. Acute Dermal Toxicity to Rabbits

When undiluted material was held in continuous 24-hour contact with abraded skin of albino rabbits of both sexes, the acute dermal LD_{50} was found to be greater than 5000 milligrams per kilogram body weight.

Classification: Core-Minimum Data

3. Eye Irritation to Rabbits

When an 0.1 milliliter volume of undiluted formulation was instilled into the conjunctival sac of the rabbit eye, a moderate degree of irritation resulted. The average score on a scale of 110 of the 24-, 48-, and 72-hour readings was 20.1 for unwashed eyes and 7.3 for washed eyes. All signs of irritation had subsided in the unwashed eyes and washed eyes at 14 and 7 days after compound administration, respectively.

Classification: Core-Minimum Data

Primary Skin Irritation to Rabbits

A slight degree of irritation resulted when 0.5 milliliter of undiluted product was held in continuous 24-hour contact with intact and abraded rabbit skin. The Primary Irritation Index was 1.1 on a scale of 8.0.

Classification: Core-Minimum Data

Based on these test results, MON 2139 NF80AA would be classified as follows:

Oral toxicity - Category IV
Dermal toxicity - Category III
Eye irritation - Category II
Skin irritation - Category IV

c. Mammalian Acute Toxicity Studies with MON 0139, Lot SSTR 11012, ML-80-261. (Monsanto, 3/17/81)

1. Acute Oral Toxicity to Rats

When the undiluted product was administered by stomach tube to fasted albino rats of both sexes, the acute oral LD_{50} was found to be greater than 5000 milligrams per kilogram body weight.

Classification: Core-Minimum Data

2. Acute Dermal Toxicity to Rabbits

When undiluted material was held in continuous 24-hour contact with abraded skin of albino rabbits of both sexes, the acute dermal LD_{50} was found to be greater than 5000 milligrams per kilogram body weight.

Classification: Core-Minimum Data

3. Eye Irritation to Rabbits

Essentially no irritation resulted when a 0.1 milliliter volume of undiluted MON-0139 was instilled into the conjunctival sac of the rabbit eye. The average score on a scale of 110 of the 24-, 48-, and 72-hour readings was 0.0 for unwashed eyes and for washed eyes.

Classification: Core-Minimum Data

4. Primary Skin Irritation to Rabbits

Essentially no irritation resulted after 0.5 milliliter of undiluted product was held in continuous 24-hour contact with intact and abraded rabbit skin. The Primary Irritation Index was 0.1 on a scale of 8.0.

Classification: Core-Minimum Data

Based on these test results, MON 0139 would be classified as follows:

Oral toxicity - Category IV
Dermal toxicity - Category III
Eye Irritation - Category IV
Skin irritation - Category IV

d. Additional Information on Formulations

The Roundup® Herbicide formulation contains 3 pounds per gallon of the glyphosate acid or 4 pounds per gallon of the isopropylamine salt of glyphosate, [redacted] gallon of a surfactant with the remainder being water and trace amounts of impurities and reaction products.

INERT INGREDIENT INFORMATION DELETED

Three formulations of Roundup Herbicide are presently registered by the agency under EPA Reg. No. 524-308. The only difference in these formulations is the surfactant and compatibility agent. They are:

1. The present formulation of Roundup Herbicide contains the surfactant [redacted] In this petition it is referred to as "Roundup".

2. A second formulation contains [redacted] as the surfactant [redacted] and [redacted] as the compatibility agent. This formulation is referred to as the W formulation. Product codes ending with W represent this formulation.

3. A third formulation contains the [redacted] surfactant with [redacted] as the compatibility agent. This formulation is referred to as the AA formulation. Product codes ending with AA represent this formulation.

The isopropylamine salt of glyphosate is also registered with the agency for use as a herbicide (EPA Reg. No. 524-326). This formulation contains no surfactant, only the active ingredient, water and related impurities. When used, it is recommended that the material be mixed with X-77 surfactant. In this petition, this formulation is referred to as either CP 70139 or MON 0139.

When the requested aquatic uses are approved by the agency, only the Roundup formulations containing the MON 8080 surfactant or the MON 0139 formulation will be labelled for these uses. The present commercial formulation of Roundup will not be labelled for use in or around aquatic sites.

7. 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.

8. Tolerances have been established under 40 CFR 180.364.

9. The published tolerances utilize 10.95% of the ADI. Unpublished, TOX approved tolerances utilize the ADI to 46.41%. (Computer printout attached)

10. No regulatory actions are pending against the pesticide and no RPAR criteria have been exceeded.

Conclusions and Recommendations:

The requested tolerances are not toxicologically supported.

Oncogenicity studies in two species are required. At least one new oncogenicity study must be submitted to support the significant increase in TMRC due to the tolerance of 0.5 ppm in potable water.

TS-769:th:TOX/HED:WDykstra:9-1-81:card 2