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CASWELL FILE

Glyphosate / Tox

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

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AUG 13 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: EPA Reg. No. 524-308; Roundup; PP# 6F3380/6H5502;
Glyphosate in/on soybean at 20 ppm

Caswell No. 661A
Project No. 2052
Record No. 172598/168897/172599

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)
and
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Hazard Evaluation Division (TS-769)

THRU: Edwin Budd, Section Head
Review Section II
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 8/12/86

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769)

William Dykstra 8/9/86

Requested Action:

Review tolerance request for the use of glyphosate on soybeans.

Background:

Tolerances have been established for the combined residues of glyphosate (Roundup; N-[phosphonomethyl] glycine) and its metabolite aminoethyl phosphonic acid in several raw agricultural commodities (40 CFR 180.364).

The Agency recently requested the SAP to consider the potential oncogenicity of glyphosate. In their 2/24/86 report, the Panel response is presented below:

"In the instance of Glyphosate, the Panel concurs that the data on renal tumors in male mice are equivocal. Only small numbers of tumors were found in any group, including those at the highest dose which appear to have exceeded the maximal tolerated dose. The vast majority of the pathologists, who examined the proliferative lesion in the male control animal, agreed that the lesion represented a renal adenoma. Therefore, statistical analysis of the data should utilize this datum. In addition, the statistical analysis shall be age-adjusted; when this is done, no oncogenic effect of Glyphosate is demonstrated using concurrent controls. Nevertheless, the occurrence of three neoplasms in high dose male mice is unusual and using historical controls is statistically highly significant. Furthermore, categorization of the oncogenic risk of Glyphosate is complicated by the fact that doses used in the rat study do not appear to have reached the maximal tolerated dose. Under these circumstances, the Panel does not believe that it is possible to categorize Glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity for humans). The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions.

Regarding the issue of using historical or concurrent controls, the Panel believes that this has to be decided on a case-by-case basis. For Glyphosate, the historical control data support that there may be reason for concern. However, the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls."

If the Agency concurs with the SAP position, glyphosate may not be considered oncogenic in male mice. If this is the case, the Delaney clause may not apply to food additive petitions (H petitions, 409 tolerances) for glyphosate.

Review:

1. No new toxicity data were submitted.

2. Section F:

Tolerances are established for combined residues of glyphosate and its metabolite aminomethylphosphonic acid on soybeans.

40 CFR 180.364

Soybeans	6 ppm
Soybeans, Forage	.15 ppm
Soybeans, Hay	.15 ppm

21 CFR 561.253

Soybean Hulls	.20 ppm

When used as directed on the requested preharvest application label, the soybean tolerances will need to be the following:

40 CFR 180.364

Soybeans	.20 ppm
Soybeans, Hay	200 ppm

When used as directed on the requested preharvest application label, a food additive tolerance will need to be the following:

21 CFR 561.253

Soybean, Hulls	.100 ppm

3. Calculation of the ADI:

The ADI is based on the NOEL of 10 mg/kg/day in the 3-generation rat reproduction study. A 100 fold safety factor was used to calculate the ADI.

$$\text{ADI} = \frac{\text{NOEL}}{100} = 10 \text{ mg/kg/day} \times \frac{1}{100}$$

$$\text{ADI} = 0.10 \text{ mg/kg/day}$$

The MPI is 6.0 mg/day for a 60 kg person.

4. Published tolerances utilize 22.81% of the ADI. Tox approved, unpublished tolerances utilize the ADI to 24.07%. The current action contributes 0.1932 mg/day to the TMRC and utilizes 3.22% of the ADI. All tolerances utilize 27.29% of the ADI (computer printout attached).

Conclusion:

Depending on the Agency's position relative to the SAP conclusions about glyphosate, the requestd tolerances may or may not be toxicologically supported.

A repeat of the chronic/oncogenic rat feeding study with glyphosate at dosages corresponding to the maximum tolerated dose and a repeat of the mouse oncogenicity study will be required to further address the MTD issue relating to the oncogenicity of glyphosate.