



GLYPHOSATE / Tox

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

MEMORANDUM:

JUL 15 1986

SUBJECT: EPA Reg. No. 524-308; Roundup; PP# 6F3408; Glyphosate
in/on Sunflowers at 0.10 ppm
Caswell No. 661A
Project No. 1882/1883
Record No. 172912/174111
Accession No. 262632

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
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THRU: Edwin Budd, Section Head
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Hazard Evaluation Division (TS-769)

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

William Dykstra 7/2/86

Major WPS
7/15/86Requested Action:

Review tolerance request for the use of glyphosate on sunflowers.

Background:

Tolerances have been established for the combined residues of glyphosate (Roundup; N-[phosphonomethyl] glycine) and its metabolite aminomethyl 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 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: Proposed tolerance. .

When used as directed on the requested label, the combined residues of glyphosate and its metabolite, aminomethylphosphonic acid, will require the sunflower tolerance to be the following:

40 CFR 180.364

Sunflower Seed 0.10.

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.

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

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

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

4. Published tolerances utilize 24.19% of the ADI. Unpublished, Tox. approved tolerances utilize that ADI to 25.52%. The current action utilizes 0.0007% of the ADI and contributes 0.000045 mg/day to the TMRC. All tolerances utilize 25.52% of the ADI (computer printout attached).

Conclusion:

Depending on the Agency's position relative to the SAP conclusions about glyphosate, the requested 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.

TOXICOLOGY BRANCH ADI PRINTOUT

Date: 06/24/86

Glyphosate (+ salts) 3gen reprod.- rat ADI = 0.100000 mg/kg/day
 Caswell #661A NOEL = 10.0000 mg/kg Safety Factor = 100
 CFR No. 180.364 LEL = 30.0000 mg/kg
 Status: TOX ADI complete 2/28/86. ORD verified 3/11/86.

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

DRAFT

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
5 Asparagus	0.200		0.14	0.000420000
6 Avocados	0.200		0.03	0.000090000
7 Bananas	0.200		1.42	0.004260000
33 Citrus fruits	0.200		3.81	0.011430000
36 Coffee	1.000		0.75	0.011250000
41 Cottonseed (oil)	15.000		0.15	0.033750000
44 Cranberries	0.200		0.03	0.000090000
49 Cucurbits	0.100		2.84	0.004260000
59 Fish, shellfish	0.250		1.08	0.004050000
60 Fruiting vegetables	0.100		2.99	0.004485000
64 Grain crops	0.100		13.79	0.020685000
66 Grapes, including raisins	0.100		0.49	0.000735000
73 Hops	0.100		0.03	0.000045000
80 Leafy vegetables	0.200		2.76	0.008280000
88 Mangoes	0.200		0.03	0.000090000
96 Molasses	20.000		0.03	0.009000000
101 Nuts	0.200		0.10	0.000300000
104 Olives	0.100		0.06	0.000090000
109 Papayas	0.200		0.03	0.000090000
115 Peanuts	0.100		0.36	0.000540000
123 Pineapple	0.100		0.30	0.000450000
126 Pome fruits	0.200		2.79	0.008370000
138 Root crop vegetables	0.200		11.00	0.033000000
143 Seed and Pod vegetables	0.200		3.66	0.010980000
146 Small fruits and berries	0.100		0.83	0.001245000
148 Soybeans (oil)	6.000		0.92	0.082800000
148 Soybeans (oil)	6.000	5F1536	0.92	0.082800000
151 Stone fruits	0.200		1.25	0.003750000
154 Sugar, cane and beet	2.000		3.64	0.109200000
162 Tea	4.000		0.07	0.004200000
184 Guava	0.200		0.03	0.000090000
198 Potable water	0.500		133.33	0.999975000
202 Palm oil	0.100		0.03	0.000045000
203 Kidney	0.500		0.03	0.000225000
210 Pistachio nuts	0.200		0.03	0.000090000
211 Liver	0.500		0.03	0.000225000

TMRC
 0.024190 mg/kg/day (60kg BW, 1.5kg diet)

% ADI
 24.189750

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
35 Coconut	0.030	2F2680	0.03	0.000013500
59 Fish, shellfish	3.000	3F2956	1.08	0.048600000
170 Wheat	0.200	3F2809	10.36	0.031080000

TMRC	% ADI
0.025518 mg/kg/day (60kg BW, 1.5kg diet)	25.517975

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
156 Sunflower	0.100	6F3408	0.03	0.000045000

TMRC	% ADI
0.025519 mg/kg/day (60kg BW, 1.5kg diet)	25.518725