



Glyphosate/Tox

JUN 23 1986

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

(51)
CASWELL FILE

005203

RECALLABLE

MEMORANDUM:

SUBJECT: EPA Reg. No. 524-343; Rodeo; PP# 3F2956; Glyphosate
in/on shellfish; Revised Section F
Caswell No. 661A
Project No. 1276/1277
Record No. 165737/165739

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
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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)

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

William Dykstra 6/9/86

WJD 6/23/86

Requested Action:

Review tolerance request for the use of glyphosate on shellfish.

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. Toxicology Branch one-liners are attached.

2. Revised Section F:

Proposed residue tolerance for shellfish of 3.0 ppm for combined residues of glyphosate and its metabolite aminomethylphosphonic acid.

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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. Calculation of the TMRC and percent of ADI utilized.

The requested tolerance is for 3.0 ppm on shellfish.

There is already a tolerance for fish/shellfish of 0.25 ppm (see computer printout)
The TMRC is as follows:

$$TMRC = \frac{\text{Tolerance}}{1.75} \times \frac{\text{Diet}}{1.5 \text{ kg/day}} \times \frac{\text{Food Factor}}{1.08/100}$$

$$TMRC = \frac{0.04455}{0.0486} \text{ mg/day}$$

$$\text{Percent increase in ADI} = \frac{TMRC}{MPI} \times 100$$

$$\text{Percent increase in ADI} = \frac{0.04455}{0.0486 \text{ mg/day}} \times 100$$

$$\text{Percent increase in ADI} = \frac{0.74}{0.81\%}$$

5. Published tolerances utilize 22.81% the ADI. Unpublished, Tox approved tolerances utilize the ADI to 23.73%. The current action utilizes ~~0.81%~~ of the ADI (computer printout attached).
0.74

*Change by Budd
6/22/86*

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: 06/10/86

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 complete. ORD complete 3/11/86.

DRAFT

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

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
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

0.022810 mg/kg/day (60kg BW, 1.5kg diet)

% ADI

22.809750

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
35 Coconut	0.030		0.03	0.000013500
148 Soybeans (oil)	4.000		0.92	0.055200000

TMRC
0.023730 mg/kg/day (60kg BW, 1.5kg diet)

% ADI
23.729975

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
59 Fish, shellfish	2.750 3.000	3F2956	1.08	0.04455 0.048600000

0.014473 TMRC
~~0.024540~~ mg/kg/day (60kg BW, 1.5kg diet)

% ADI
~~24.539975~~
24.473000

changes by
Budd
6/22/86