



Glyphosate / Tox

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

59
CASWELL FILE

release
005651

JAN 12 1987

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Glyphosate; Roundup; EPA Reg. NO. 524-308;
Addendum to one year dog study with glyphosate; PP#
6F3380/6H5502; Glyphosate in/on soybeans; revised
Section F; and amended label text

Caswell No. 661 A
Record No. 186082/186083/186084
Project No. 7-0230
Accession No. 264334

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)
and
Residue Chemistry Branch
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 1/9/87

W. J. W. B. 1/10/87

Requested Action:

Review revised Section F, amended label text and addendum
to one-year dog study with glyphosate.

Background:

1. PP#6F3380/6H5502

Monsanto submitted a Roundup herbicide petition that
requested Agency approval to apply Roundup preharvest to
soybeans. This submitted petition included a request to amend
the current 15 ppm glyphosate tolerance on soybean hay to 200
ppm.

At this time, Monsanto requests to amend the submitted
(2/21/86) petition by deleting the 200 ppm glyphosate soybean
hay tolerance request and modifying the submitted preharvest
soybean label text to restrict against feeding or grazing
soybean hay or forage from preharvest soybean treated areas.

2. One-year dog study

With respect to the one-year dog study with glyphosate, it was previously concluded in memo of 3/12/86 from W. Dykstra to R. Taylor that "the absolute and relative pituitary weights of the mid-and high-dose male dogs are suggestive of a possible compound-related effect. The registrant is requested to further address the pituitary findings and the relationship to treatment."

The registrant is responding to that memo with this addendum.

Conclusions and Recommendations:

1. In PP#6E3424, RCB states that "RCB can reach no final conclusion regarding the likelihood that contaminants in the technical product will or will not result in a residue problem until issues involving identification/quantitation of nitrosamine presented in Glyphosate registration Standard have been resolved." This same issue regarding nitrosamines in technical glyphosate also applies to the current petition for soybeans.

Toxicology Branch requires that the identification/quantitation of nitrosamine be determined for technical glyphosate before the requested tolerances are granted.

The revised Section F has no effect on the TMRC or percent ADI utilized. (review of 8/13/86 is attached). Toxicology Branch requests that RCB address the acceptability of the amended label.

2. Toxicology Branch concludes that the apparent decreases in the absolute and relative pituitary weights of the mid-and high-dose male dogs are not compound-related. The NOEL for the study is the high-dose of 500 mg/kg/day. The study is acceptable as guideline data.

Review:

1. PP# 6F3380/6H5502: Revised Section F

Proposed Tolerances

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

005651

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

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

2. In memo of March 12, 1986, it was concluded that the decrease in the absolute and relative pituitary weights of the mid- and high-dose male dogs are suggestive of a possible compound-related effect. In response to this conclusion, the present addendum (Accession No. 264334) was submitted by the registrant. In the memo of 3/12/86 of the one-year dog study, the following data were presented:

<u>Pituitary in Males</u> <u>Weight (gram)</u>				
<u>Dogs</u>	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
1)	0.088	0.079	0.066	0.064
2)	0.096	0.069	0.050	0.070
3)	0.076	0.090	0.061	0.055
4)	0.080	0.073	0.054	0.062
5)	0.083	0.089	0.071	0.074
6)	<u>0.079</u>	<u>0.077</u>	<u>0.067</u>	<u>0.080</u>
Mean	0.084	0.080	0.062	0.068
S.E.	0.003	0.003	0.003	0.004

- 4 -

Relative pituitary weight are shown below:

Percent Relative to Terminal Body Weight

Pituitary in Males

<u>Dogs</u>	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
1)	0.00073	0.00057	0.00061	0.00059
2)	0.00106	0.00056	0.00047	0.00064
3)	0.00069	0.00066	0.00053	0.00061
4)	0.00065	0.00063	0.00054	0.00061
5)	0.00090	0.00099	0.00068	0.00069
6)	<u>0.00068</u>	<u>0.00066</u>	<u>0.00059</u>	<u>0.00060</u>
Mean	0.00079	0.00066	0.00057	0.00062

In the registrant's letter of August 1, 1986 from F.A. Ruecker, the following information is presented.

"After a review of the pituitary weight data for the 1-year glyphosate oral toxicity study in dogs (EHL No. 830116) it is my opinion that there is no conclusive evidence that the decreased mean pituitary weight for high and mid dose males can be attributed to compound administration for the following reasons:

1. The magnitude of the weight decrease is greater for the mid dose when compared to high dose (0.0222 g. vs. 0.0162 g.) therefore there is no apparent dose relationship.
2. There is no apparent microscopic lesion present in the pituitary which would be expected to be a correlate of the decreased weight changes (atrophy or necrosis of pituicytes).

3. Since the pituitary exerts hormonal control over a variety of endocrine organs, one might expect that any lesions which would reduce pituitary weights could possibly effect the hormonal output of the pituitary and thus have effects on the organs under pituitary control (thyroid, testes, adrenals, etc.). There were no weight changes or microscopic lesions observed for any of these organs.
4. There were no comparable pituitary weight differences for females when compared to controls.
5. Finally, a review of 3 other EHL-conducted, 1 year, oral, toxicity studies in dogs (81124, 82165, 84056) showed a pituitary weight range for male controls from .064 to .072 g., and inter-group mean pituitary weight range of .062- 0.088 g., .059- 0.071 g. and .070-. 083 g., for each of the studies, respectively. It should be noted that the mean pituitary weights for control males (.084 g.) in the 830116 study are higher than have been observed for control males in these other studies while the mean weights for the mid and high dose males are closer to the historical mean weight ranges for controls. Additionally the mean pituitary-to-body weight ratio of .001% for each group in the 830116 study is not different from that observed in all groups in the other three studies. These data strongly suggest that the apparent decrease in pituitary weights for the mid and high dose males in the 830116 study may be actually an aberration due to an unusually high mean weight for the control males."

Conclusion:

Toxicology Branch concludes that the apparent decreases in absolute and relative pituitary weights of the mid- and high-dose male dogs are not compound-related.

The NOEL for the study is the high-dose of 500 mg/kg/day.

Classification: Guideline.