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

Revised to DEB 10/25/89 to clarify pts 4 & 9 based on review of GF-3380

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

FEB - 1 1989

MEMORANDUM

SUBJECT: PP#8F3673/EPA Registration No. 524-308 - Glyphosate for Use In or On Field Corn - MRID Nos. 405026-01, -03, and -05 - Evaluation of Analytical Method and Residue Data

DEB No.: 4289

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and

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THRU: Charles L. Trichilo, Ph.D., Chief
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Monsanto Company requests that the following tolerances be established for residues of glyphosate [N(phosphonomethyl)glycine] on corn:

Corn grain	1 ppm
Corn fodder	20 ppm
Corn forage	20 ppm

Monsanto should confirm that the above tolerances refer to the combined residues of glyphosate and its metabolite aminomethylphosphonic acid (AMPA).

1/20

Tolerances for the combined residues of glyphosate and AMPA have been established under 40 CFR 180.364(a) for a number of raw agricultural commodities (RACs) at levels varying from 0.1 to 200 ppm. Tolerances for the combined residues of glyphosate and AMPA resulting from application of glyphosate isopropylamine salt (for herbicidal purposes) and/or the sodium sesqui salt (for plant growth regulator purposes) have been established under Section 180.364(b) in fish at 0.25 ppm; liver and kidney of cattle, goats, hogs, horses, poultry, and sheep at 0.5 ppm; and sugarcane at 2.0 ppm.

Tolerances of 0.1 ppm have been established on the various crop groupings under Section 180.364(c) for the combined residues of glyphosate and AMPA resulting from the use of irrigation water containing residues of 0.5 ppm. If a higher tolerance has been set elsewhere [Section 180.364(a) or (b)], the higher tolerance applies. [Note to the PM: The wording of Section 180.364(c) is in error. The word "no" should be deleted from the final sentence of the subsection.]

There is currently a tolerance of 0.1 ppm for corn (Section 180.364(a) - grain crops) and 0.2 ppm for corn forage (same section - grasses, forage). Therefore, Monsanto is requesting a tenfold increase in the tolerance for grain and a hundredfold increase in the tolerance for forage and fodder.

The Product Chemistry and Residue Chemistry Chapters for the Glyphosate Registration Standard were issued on May 31, 1985.

Conclusions

1. Monsanto should confirm that its proposed tolerances refer to the combined residues of glyphosate and its metabolite AMPA.

2. The presence of nitrosamines is not a residue problem in Roundup®.

3a. The petitioner should submit a revised Section B which combines the first two paragraphs of its proposed label to read as follows:

> Apply up to . . . spray volume in 3 to 20 gallons of water per acre for ground applications or 3 to 10 gallons of water per acre for aerial applications.

3b. The label recommends use of ammonium sulfate as an adjuvant. Residue levels of glyphosate may be higher as a result of this use. If ammonium sulfate was not used as an adjuvant in the residue trials, the petitioner should either submit a revised Section B which stipulates that ammonium sulfate not be used when glyphosate is applied to preharvest corn or submit additional residue data reflecting use of ammonium sulfate as an adjuvant in glyphosate. (In the latter case, residue data from preharvest application of glyphosate to other crops may be acceptable if the data show no higher glyphosate residue when ammonium sulfate is present.)

4a. The nature of the residue in corn is adequately understood. The residue to be regulated is glyphosate, per se, and its metabolite AMPA.

4b. The nature of the residue in animals is not adequately understood. The Registration Standard has required additional studies in ruminants and poultry.

5a. The HPLC method used to obtain the residue data is undergoing EPA method validation. DEB will not delay any tolerance recommendations pending completion of the method validation.

5b. Neither glyphosate nor AMPA has been tested under FDA's multiresidue protocols. On the basis of FDA's "Decision Tree for MRM Testing" (Attachment 1), Monsanto should carry out the appropriate tests for glyphosate and AMPA.

5c. There is an analytical method in PAM II for enforcing glyphosate tolerances.

6a. Storage stability studies on a number of crops are sufficient to support the residue analyses of this petition.

6b. Residue data on corn grain and fodder show significantly higher glyphosate levels at 14 days than at 7 days. Monsanto should provide an explanation for this phenomenon.

6c. Forage was not analyzed. Perhaps, after treatment with glyphosate, forage as such could not exist. Monsanto should provide an explanation.

7. Proposed tolerances of 1.0 ppm for grain and 20 ppm for fodder are inadequate. The petitioner should submit a revised Section F proposing tolerances for the combined residues of glyphosate and AMPA of 2.0 ppm for corn grain and 35 ppm for corn forage and fodder.

8a. The submitted fractionation study shows that glyphosate residues concentrate slightly in fat-free meal and are present at negligible concentrations in oil or soapstock. No revision of the tolerance expression is required because of this study.

8b. Corn grain was not dry-milled into either grits or flour. A new processing study should be carried out in which these commodities are prepared. There is no need to process the corn into the items that have already been analyzed.

8c. Results from the preliminary wet-milling study strongly indicate that glyphosate residues will not concentrate in starch, or crude and refined oils.

9. ✓ Based on the 30-day feeding studies in cattle, it appears that existing tolerances for glyphosate residues in animal products may be exceeded due to the proposed use of glyphosate. We defer final comment until the nature of the residue in animals is adequately understood.

10. An International Residue Limit Status sheet is appended to this review. There is a Codex tolerance of 0.05 ppm for residues of glyphosate, per se, on maize. There is a Canadian negligible residue limit of 0.1 ppm for residues of glyphosate on all food crops. However, residue levels of glyphosate from the proposed use are far in excess of those permitted by Codex and Canada and compatibility cannot be achieved.

Recommendations

DEB recommends against the proposed tolerances for the reasons given in Conclusions 1, 3a, 3b, 4b, 5b, 6b, 6c, 7, 8b, and 9 as follows:

1. Monsanto should confirm that its proposed tolerances refer to the combined residues of glyphosate and its metabolite AMPA.

3a. Monsanto should submit a revised Section B which combines the first two paragraphs of its proposed label to read as follows:

> Apply up to . . . spray volume in 3 to 20 gallons of water per acre for ground applications or 3 to 10 gallons of water per acre for aerial applications.

3b. If ammonium sulfate was not used as an adjuvant in the residue trials, Monsanto should either submit a revised Section B which stipulates that ammonium sulfate not be used when glyphosate is applied preharvest to corn or submit additional data. (In the latter case, residue data reflecting preharvest application of glyphosate to other crops may be acceptable if the data show no increase in glyphosate residues when ammonium sulfate is used.)

4b. Additional metabolism studies in ruminants and poultry, as required by the Registration Standard, should be submitted.

5b. Glyphosate and AMPA must be tested under FDA's multiresidue protocols. FDA's "Decision Tree for MRM Testing" (Attachment 1) should be used as a guide to determine the appropriate tests.

6b. Monsanto should explain why glyphosate residues in corn grain and fodder were significantly higher after a 14-day PHI than at a 7-day PHI.

6c. Monsanto should explain why corn forage was not analyzed.

7. Monsanto should submit a revised Section F proposing tolerances for the combined residues of glyphosate and AMPA of 2.0 ppm for grain and 35 ppm for forage and fodder.

8b. Monsanto should conduct an additional dry-milling study in which grain is processed into grits and flour.

9. Although it appears that tolerances in animal products may have to be raised as a result of the proposed use of glyphosate, DEB will defer comment until the nature of the residue in animals is adequately understood.

Detailed Considerations

Manufacturing Process and Formulation

The Registration Standard identified a number of data gaps, including an adequate description of the manufacturing process for the unregistered technical isopropylamine glyphosate salt used to prepare the commercial formulation. The complete description of the manufacturing process was subsequently submitted by Monsanto in two reports (PP#6F3380/FAP#6H5502, MRID Nos. 401558-01 and -02. See memorandum of J. Stokes, September 1, 1987).

The glyphosate formulation of this petition is known commercially as Roundup® (EPA Registration No. 524-308-AA) and contains 4 lb of the isopropylamine salt per gallon, equivalent to 3 lb glyphosate active ingredient/gallon.

Analysis of technical glyphosate and the isopropylamine and sodium sesqui salts indicated the presence of N-nitrosoglyphosate. Toxicology Branch (TB) was requested to review the N-nitrosoglyphosate levels and determine whether they were of toxicological concern (memorandum of J. Stokes, September 1, 1987). TB responded that N-nitrosoglyphosate levels in glyphosate were not of toxicological concern (W. Dykstra, memorandum of February 11, 1988). In addition, four other nitrosamines were not detected in Roundup® at levels of 0.05 or 0.1 ppm (PP#6E3424, memorandum of W.T. Chin, February 25, 1988). We conclude that the presence of nitrosamines in Roundup® is not a significant problem.

Proposed Use

Roundup® is to be used for control or suppression of annual and perennial weeds prior to the harvest of corn. Do not apply to sweet corn.

> Apply up to but no more than 1 quart per acre of this product plus 0.5 to 1 percent nonionic surfactant by total spray volume in 3 to 20 gallons of water per acre.
>
> For ground applications, use this product in 3 to 20 gallons of water per acre. For aerial applications, use this product in 3 to 10 gallons of water per acre.
>
> Apply this product after maximum kernel fill is complete and the crop is physiologically mature (black layer formation). Make applications when the

> moisture content of the corn is 35 percent or less.
>
> Allow a minimum of 7 days between application and harvest.

We recommend that the first two paragraphs above be combined to read the following:

> Apply up to . . . spray volume in 3 to 20 gallons of water per acre for ground applications or 3 to 10 gallons of water per acre for aerial applications.

Ammonium sulfate (17 lb/100 gal water) may be added to increase performance of Roundup. As noted in C. Deyrup's Memorandum of Telecon with Monsanto, June 8, 1988, foliar use of ammonium sulfate with glyphosate may lead to increased glyphosate levels in crops. If ammonium sulfate was not used as an adjuvant in the residue trials discussed below, the petitioner should either submit a revised Section B which stipulates that ammonium sulfate not be used when glyphosate is applied preharvest to corn or submit additional residue data reflecting application of glyphosate in the presence of ammonium sulfate. (In the latter case, residue data from preharvest application of glyphosate to other crops may be acceptable if the data show no higher glyphosate residues when ammonium sulfate is present.)

Nature of the Residue

Plants

No new metabolism studies have been submitted in this petition. Metabolism studies on a variety of crops (citrus, coffee, pome fruits, alfalfa, sugarcane, grapes, soybeans, cotton, wheat, and corn) have been submitted in previous petitions and are discussed in the Registration Standard. The studies show that uptake of glyphosate or its metabolite, AMPA, from soil is limited (0.1 to 0.2%), but the residues which are taken up are translocated. Uptake is increased in hydroponically grown plants in media treated with labeled glyphosate or AMPA. Foliarly applied glyphosate is readily absorbed and translocated to untreated parts of plants including the fruits of grapes, apples, pears, citrus, and coffee.

Monsanto submitted a study of the uptake and metabolism of glyphosate by corn (PP#4G1444). Cotton, soybeans, and wheat were also examined in this study. [^{14}C-methane]-glyphosate and, in separate experiments, [^{14}C]AMPA were applied to the soil surface in pots 1 week after seeding

the four crops. Eight weeks after treatment, the above-ground portions of corn, cotton, soybeans, and wheat, respectively, contained 0.05, 0.28, 0.07, and 0.12 percent of the applied ^{14}C, calculated as glyphosate. The maximum uptake of ^{14}C residues from [^{14}C]AMPA application was 0.04 percent.

In another experiment, the four crops were germinated in sand culture and transferred to hydroponic tanks containing nutrients and [^{14}C-methane]glyphosate at ca. 2.5 ppm (soybeans and cotton) or 0.60 ppm (corn and wheat). Plants were 2 weeks old at the time of treatment. At the end of the incubation period--28 days for soybeans, corn, cotton; 10 days for wheat--shoot and root samples were extracted by vigorous stirring in water for 1 to 4 hours. Additional samples were sequentially extracted with water, 0.5 M NH_4OH, and 0.5 M HCl. Data for corn are given in the following table (from PP#4G1444, Accession No. 118397, Table 126).

Table 1

Percentage Composition of ^{14}C in Corn Hydroponically Treated with [^{14}C-Methane]Glyphosate

	H_2O Extractable	Unextract-able	Glyphosate	AMPA	Natural Products	Inde-term.
Corn Tops	73.4	26.6	21.1	27.9	4.0	20.0
Corn Roots	64.3	35.7	46.1	4.4	2.0	11.8

In contrast with the other treated crops, we note that the residue from corn tops contained more metabolite than parent.

Sequential extraction (H_2O, 0.5 M NH_4OH, 0.5 M HCl) released almost all ^{14}C in corn tops (96.6%) and most of the ^{14}C in roots (88.5%). No further characterization was undertaken, however.

There have been no studies on corn in which glyphosate was foliarly applied. However, numerous foliar application studies have been completed on various RACs, including grapes, coffee, dwarf citrus, walnut, almond and pecan trees, apples and pears, alfalfa and fescue, sugar beets, and sugarcane (Registration Standard, pages 13-27). In all cases, parent was the predominant constituent of the extractable residue. AMPA was found in much lesser quantities, and N-(methylamino)-N-methylphosphonic acid was detected in some of the studies. Additionally, the completed residue studies on corn (*vide infra*) demonstrate that glyphosate, *per se*, is present in much greater quantities than is AMPA. We are confident that the metabolism of glyphosate when foliarly

applied to corn is not dissimilar to that in other foliarly treaced crops.

The nature of the residue in/on corn is adequately understood. The residue to be regulated is parent glyphosate and its metabolite AMPA.

Animals

Metabolism in animals has been studied using rats, rabbits, catfish, and lactating cow. In the latter study, one lactating Holstein cow was fed 10 ppm of glyphosate in gelatin capsules over a 7-day dosing period. Milk was sampled twice daily, and total urine and feces radioactivity was collected every 24 hours. On the eighth day, the cow was sacrificed and tissues analyzed for total radioactivity.

^{14}C-Activity in milk increased from 0.015 ppm after 1 day to 0.023 ppm by day 6. Residues in urine increased from 0.3 ppm on day 1 to 1.07 ppm on day 6. A plateau level was reached by day 2 (0.8 ppm). Residue levels in feces increased from 3.2 ppm on day 1 to 6.6 ppm on day 6, and levels appeared to plateau by day 3. ^{14}C-Activity in tissues were 0.20 ppm in kidney, 0.11 ppm in rumen fluid, 0.05 ppm in liver, 0.046 ppm in muscle, 0.022 ppm in fat, and 0.006 ppm in blood. Residues were not characterized (Registration Standard, pages 29-37).

The Registration Standard has required additional metabolism studies in ruminants and poultry. Animals must be dosed for 3 days with glyphosate, and the distribution, characterization, and quantification of residues must be determined in eggs, milk, muscle, fat, kidney, and liver.

The nature of the residue in animals is not adequately understood.

Analytical Method

Monsanto's analytical method appears as Appendix E in Volume 2 of the petition (MRID No. 405026-01). The method is titled "Analytical Residue Method for N-Phosphonomethyl Glycine and Aminomethylphosphonic Acid in Raw Agricultural Commodities." No authors are listed. Results of an interlaboratory study on this method have been published (Cowell, J.E., et al., J. Agric. Food Chem., 1986, 34(6):955-60).

Samples are ground frozen and then extracted with a mixture of chloroform and 0.1 N HCl in a 1/3 (v/v) ratio. An exact volume of the aqueous layer is decanted and transferred to a Chelex 100 column in the Fe(III) form. The sample is

eluted with deionized water. Glyphosate and AMPA are then eluted with 6 N HCl. The eluate is further purified using an AG 1X6 anion exchange column, which removes iron (III). Final analysis is by HPLC using a fluorescence detector specific for compounds which produce a fluophor upon reaction with o-phthalaldehyde (OPA) and mercaptoethanol (MERC). (An Aminex A-9 cation exchange column is used to separate the glyphosate and AMPA for postcolumn derivatization. Glyphosate is then oxidized to glycine by calcium hypochlorite, and both glycine and AMPA are coupled with OPA-MERC in separate experiments to give fluophors detected by excitation at 340 nm and emission at 455 nm.)

Average recoveries for corn grain and fodder are given in Table 2. Fortification levels varied from 0.04 to 7 ppm for grain and 0.04 to 26 ppm for fodder.

Table 2

Percent Recoveries

Matrix	Glyphosate	AMPA
Corn Grain	83.1 ± 5.3	88.2 ± 7.6
Corn Fodder	89.6 ± 14.1	88.0 ± 8.9

Average recoveries for blind-fortified samples, (fortified at Monsanto and sent to the contract analytical lab as unknowns) were 75.1 ± 21.2 and 92.6 ± 5.5 percent for glyphosate and AMPA, respectively, in grain and 73.9 ± 7.0 and 47.2 ± 22.2 percent for glyphosate and AMPA, respectively in fodder. Monsanto has no explanation for the low AMPA recoveries but suggests that there may have been a human error in the spiking. Considering that recoveries of glyphosate, the primary analyte, are acceptable for both grain and fodder, the recoveries of AMPA were acceptable in grain, and the known fortification recoveries were acceptable, DEB considers the validation acceptable.

The HPLC method above is undergoing EPA method validation. The current method given in PAM II, a GLC method, is considered too long to be satisfactory for enforcement purposes. As in the case of soybeans, DEB will not delay any tolerance recommendations pending completion of the method validation (PP#6F3380/FAP#6H5502, memorandum of J. Stokes, September 1, 1987).

Glyphosate and AMPA have not to our knowledge been tested under FDA's multiresidue protocols [40 CFR 158.125(b)(15)]. On the basis of FDA's "Decision Tree for

MRM Testing" (Attachment 1), Monsanto should carry out the appropriate tests for glyphosate and AMPA.

Residue Data

Storage Stability

Samples collected in the field were frozen after harvest, packed in dry ice and shipped to Monsanto's labs, where they were stored in a freezer at < 0 °F. Samples were also shipped in dry ice to Craven labs for analysis, and Craven labs kept the samples frozen as well. Grain samples were analyzed 10 to 13 months after harvest. The corresponding range for fodder samples was 12 to 15 months.

Adequate storage stability data are available for glyphosate and AMPA in/on soybeans. Storage stability data for soybean grain from 9 to 45 months and soybean hay from 9 to 46 months have been previously submitted. Temperature of storage was -20 °C. Recoveries were acceptable (PP#6F3380/ FAP#6H5502, memorandum of J. Stokes, September 1, 1987). The Registration Standard had previously concluded (July 15, 1985) that storage stability was inadequate as stability of residues of glyphosate and AMPA in plants was ascertained for only a 7-month period of storage.

In this petition, Monsanto has submitted a status report dated January 1988 concerning its ongoing storage stability studies. The report is titled "Storage Stability of Glyphosate In Crops and Water - Status Report," Job No. 066300. The author is M.G. Mueth. The study has been assigned MRID No. 405026-05.

Corn grain, soybean forage, sorghum straw, clover, tomatoes, and water were examined; and both endogenous and exogenous fortified samples were used in the study. The endogenous samples were originally analyzed in conjunction with the individual crop studies from which they were taken. The exogenous samples were fortified check samples which were stored frozen and analyzed at various intervals. These latter samples were included to cover the period from crop harvest through the first analysis of the endogenous samples.

In the water study, water samples were fortified at 500 ppb with both glyphosate and AMPA and then kept in frozen storage until analysis at 0, 3, 6, 9, and 12 months.

RACs were analyzed by the HPLC method described above. The water was analyzed by a slightly different procedure. Extraction and chelation steps were eliminated and EDTA added to complex trace metals in environmental water.

Endogenous residues showed no significant decline over the period from the first analysis to the second. These periods are: corn grain, 10 months; soybean forage, 25 months; sorghum straw, 38 months; clover, 44 months; and tomatoes, 44 months. The study is ongoing, and at the end of 1989 a final report will be issued.

Exogenous residues generally showed no decline over a 3-month period. A decline is evident in the AMPA levels in sorghum straw (12%) and clover (13%). Studies will be continued to 30 months.

Both glyphosate and AMPA are stable in water for up to 12 months under frozen storage. The study will be continued to 24 months.

We consider these data, in their entirety, adequate to support the residue studies in this petition.

Residue Trials were held in 11 States, including the top seven corn-producing States in 1984 (Agricultural Statistics, 1985). In each trial, Roundup herbicide was applied by ground (3 locations) or aerial applications at 0.38 and 0.75 lb ai/A. Grain and fodder were harvested after treatment. PHIs were 7 or 14 days. Samples were analyzed at Monsanto's labs in St. Louis, MO. Our residue chemistry guidelines stipulate that corn grain, forage, and fodder should be analyzed. Monsanto has analyzed grain and fodder only. We consider fodder to be the dried plant without grain, and forage to be the whole green plant. The petitioner should explain why forage was not analyzed. Is it because no forage as such would exist after treatment with glyphosate, which could act as a desiccant?

Results, corrected for recoveries, are given for grain and fodder in Tables 3 and 4. No AMPA was detected in corn grain at a detection limit of 0.05 ppm.

Table 3

Results of Analyses of Preharvest Corn Grain

Location	lb ai/A	PHI = 7 Days	PHI = 14 Days
Millsboro, DE	0.38	0.50 ppm	0.40 ppm
	0.75	0.89	0.65
Boling, TX	0.38	0.28	0.24
	0.75	0.51	0.87
Hansen, ID	0.38	< 0.05	< 0.05
	0.75	< 0.05	< 0.05

Table 3

Results of Analyses of Preharvest Corn Grain (cont'd)

Location	Lb ai/A	PHI = 7 Days	PHI = 14 Days
Leroy, MN	0.38	< 0.05	< 0.05
	0.75	0.09	0.09
Madison, IN	0.38	< 0.05	< 0.05
	0.75	< 0.05	< 0.05
Sheldon, IL	0.38	0.10	0.14
	0.75	0.23	0.28
Wahoo, NE	0.38	0.40	0.43
	0.75	0.94	1.19
West Liberty, IA	0.38	0.15	0.26
	0.75	0.61	0.56
Lafayette, OH*	0.38	< 0.05	< 0.05
	0.75	0.13	0.11
Milton, WI*	0.38	< 0.05	0.05
	0.75	0.70	0.57
Olanta, SC*	0.38	0.65	0.58
	0.75	1.77	2.04

*Ground application. Roundup was air-applied in the other studies.

Table 4

Results of Analysis of Corn Fodder

		Glyphosate		AMPA	
Location	lb ai/A	PHI = 7 Days	PHI = 14 Days	PHI = 7 Days	PHI = 14 Days
Millsboro, DE	0.38	2.73 ppm	3.73 ppm	0.06 ppm	0.09 ppm
	0.75	4.05	5.48	0.09	0.11
Boling, TX	0.38	8.68	8.30	0.27	0.24
	0.75	15.8	29.7	0.38	0.67
Hansen, ID	0.38	2.10	0.47	< 0.05	< 0.05
	0.75	1.32	2.74	< 0.05	< 0.05
Leroy, MN	0.38	2.25	1.35	0.07	< 0.05
	0.75	3.69	2.51	0.10	0.09

Table 4

Results of Analysis of Corn Fodder (cont'd)

Location	lb ai/A	Glyphosate		AMPA	
		PHI = 7 Days	PHI = 14 Days	PHI = 7 Days	PHI = 14 Days
Madison, IN	0.38	< 0.05	0.59	< 0.05	< 0.05
	0.75	< 0.05	0.30	< 0.05	< 0.05
Sheldon, IL	0.38	0.75	0.99	< 0.05	< 0.05
	0.75	1.56	1.42	< 0.05	< 0.05
Wahoo, NE	0.38	2.37	2.45	0.06	0.06
	0.75	3.99	7.52	0.08	0.16
West Liberty, IA	0.38	3.61	1.90	0.11	0.06
	0.75	1.70	6.53	0.06	0.14
Lafayette, OH	0.38	5.56	4.15	0.07	0.07
	0.75	4.24	4.63	0.05	0.07
Milton, WI	0.38	< 0.05	0.25	< 0.05	< 0.05
	0.75	7.01	10.05	0.13	0.14
Olanta, SC	0.38	3.23	4.44	< 0.05	0.09
	0.75	15.6	22.0	0.23	0.30

The petitioner should explain why glyphosate levels found 2 weeks after sampling are significantly higher than corresponding levels found 1 week after sampling. Have the dates been reversed?

Data from five field trials in TN, IA, IL, and SC were submitted in PP#3G2961, Accession No. 071937, and evaluated in S. Malak's memorandum of December 19, 1983. Glyphosate was ground-applied at rates of 0.75 to 4.5 lb ai/A. After application at 0.75 to 1.50 lb ai/A, residues of glyphosate ranged from < 0.31 to 17.1 ppm in/on corn fodder. PHIs varied from 7 to 15 days. These results are consistent with those in the current petition.

Data were also reported in PP#4G1444 but reflected preemergent application and are not relevant to this petition. Not surprisingly, residues were much lower (< 0.05 ppm in grain).

From these data, DEB concludes that the proposed tolerances of 1.0 ppm for glyphosate residues in/on grain and 20 ppm for glyphosate residues in/on fodder are inadequate. The petitioner should submit a revised Section F in which the tolerance for the combined residues of glyphosate and AMPA

in/on grain is 2.0 ppm and the tolerance for the same residues in/on fodder is 35 ppm. (The latter tolerance is based on the 14-day PHI data.)

Fractionation Study (MRID No. 405026-03)

Monsanto has submitted results of a corn fractionation study in a report titled "Glyphosate Residues in Corn Grain Fractions Following Preharvest Applications to Corn with Roundup® Herbicide," September 1987, Laboratory Project No. MSL-6917. The author is J.L. Kunstman.

Samples of grain from three of the above residue trials (NE, WI, and SC) were fractionated into fat-free meal, crude oil, refined oil, and soapstock fractions. Samples from the same field trials were also subjected to the initial stages of the wet fractionation process for corn, producing fractions of steeped water and steeped corn grain. Results, corrected for recovery, are given in Tables 5 and 6. Because no AMPA residues were found in any of the grain samples, fractions were not analyzed for this metabolite.

Table 5

Dry Fractionation Process

		ppm Glyphosate				
	lb ai/A	Whole Grain	Fat-Free Meal	Crude Oil	Refined Oil	Soapstock
NE	(7-day PHI)	0.75	0.94	1.1	< 0.05	Not analyzed
	(14-day PHI)	0.75	1.19	1.22	< 0.05	Not analyzed
WI	(7-day PHI)	0.75	0.7	0.82	< 0.05	< 0.05	< 0.05
	(14-day PHI)	0.75	2.04	2.07	< 0.05	< 0.05	< 0.05

Results in Table 5 show that glyphosate residues are not transferred into any of the oil or soapstock fractions, but remained in the grain after extraction. Higher residues in fat-free meal are expected because of loss of oil from the sample and a small loss of water during fractionation.

Dry-milled products from corn that should be analyzed include grits, meal, flour, and crude and refined oils (C. Trichilo, memorandum of March 21, 1985). Monsanto apparently did not process corn into grits or flour. A new processing study should be carried out in which corn is processed into grits and flour. (There is no need to process corn into meal, oil, or soapstock in the additional study.)

Rather than carry out a full wet fractionation processing study, Monsanto has merely completed the first

stage in an attempt to demonstrate that the residue reduction due to steeping water will more than compensate for any subsequent concentration of residues later in the process.

Table 6

Wet Fractionation Process

	lb ai/A	ppm Glyphosate	
		Steeped Grain	Steeped Water
NE (7-day PHI)	0.75	0.11 (0.14)*	0.16 (0.85)*
(14-day PHI)	0.75	0.24 (0.27)	0.16 (0.67)
WI (7-day PHI)	0.75	< 0.05 (< 0.08)	0.10 (0.67)
SC (14-day PHI)	0.75	0.34 (0.23)	0.24 (0.59)

*Numbers in () are concentration factors after taking into account sample dilution. In the above cases, 200 g grain was steeped resulting in 1000 mL steeped water for each sample. Final grain weights were from top to bottom 235, 270, 225, and 274 g, respectively.

Example: Concentration factor for NE (7-day PHI):

0.11/0.94 (Table 5) x 235/200 = 0.14 for steeped grain.

0.16/0.94 x 1000/200 = 0.85 for steeped water.

The first example indicates that residue in grain dried after steeping would be reduced from 0.94 to 0.14 ppm. Based on the fractionation results from the dry-milling study, we can conclude that further fractions of the wet-milled grain would not increase glyphosate levels to those in the initial corn grain.

Residues in starch and crude or refined oil will almost certainly be lower than initial residues in corn grain. Therefore, further processing to these commodities is unnecessary.

Meat, Milk, Poultry, and Eggs

Tolerances of 0.5 ppm have been established under 40 CFR 180.364(b) for combined residues of glyphosate and its metabolite AMPA in the liver and kidney of cattle, goats, hogs, horses, poultry, and sheep.

Thirty-day feeding studies with poultry, swine, and dairy cows were carried out in conjunction with PP#5F1536. Dose levels were 10, 30, and 100 ppm of a 3:1 mixture of glyphosate and AMPA.

Residue levels in poultry and eggs were nondetectable (< 0.05 ppm for glyphosate and AMPA) except for levels in liver from birds fed at 100 ppm. These levels were 0.05 to 0.06 ppm glyphosate and 0.08 to 0.10 ppm AMPA. Kidney levels were not reported.

Residue levels in fat and muscle of swine were nondetectable, but combined residues of 0.16 ppm were found in liver at the highest feeding level. Levels in kidney were higher: 0.47 ppm at the 30 ppm dose level and 1.13 ppm at the 100 ppm dose level.

Results in cattle were similar: detectable residues (0.14 ppm) in liver at the 100 ppm dose level and higher levels in kidney (0.70 ppm at the 30 ppm dose level; 1.64 ppm at the 100 ppm dose level).

Based on the cattle feeding study, we estimate that a dietary level of about 20 ppm glyphosate residues could yield residues in kidney in excess of the 0.5 ppm tolerance. Such levels would probably not be obtainable using corn grain as a feed item but are conceivable with corn forage or fodder. For example, the diet listed in Table 7 would produce a glyphosate residue level of 20 ppm if all commodities had residues at their proposed tolerance.

Table 7

	Tolerance	% Diet of Beef Cattle[a]	Contribution to Daily Diet
Corn Silage	20 ppm[b]	30	6 ppm
Alfalfa Forage	20 ppm[c]	50	10 ppm
Clover	20 ppm[c]	20	4 ppm
			Total = 20 ppm

[a]Percentages in the diet were taken from L.E. Harris, Guide for Estimating Toxic Residues in Animal Feeds or Diets, January 1975.

[b]Proposed tolerance. We assume here that levels in silage approximate those in forage and fodder.

[c]10% spot application: 200 ppm x 10% = 20 ppm (PP#1F2518).

Since the proposed tolerance of 20 ppm in corn forage is inadequate, a more appropriate tolerance (35 ppm) could result in residues exceeding 0.5 ppm in kidney.

We note that the proposed tolerances for soybean RACs could also result in glyphosate residues exceeding their tolerances in animal products. (PP#6F3380/6H5502: soybeans, 20 ppm; soybean hay, 200 ppm; soybean hulls, 100 ppm. See memorandum of W.T. Chin, October 24, 1986.)

We conclude that tolerances for glyphosate residues in animal products may have to be raised. At the present time any action would be premature until the nature of the residue in animals is adequately understood.

Other Considerations

An International Residue Limit Status sheet is appended to this review. There is a Codex tolerance of 0.05 ppm for residues of glyphosate, per se, on maize. There is a Canadian negligible residue limit of 0.1 ppm for residues of glyphosate on all food crops. However, residue levels of glyphosate from the proposed use are far in excess of those permitted by Codex and Canada and compatibility cannot be achieved.

Attachment 1: FDA's "Decision Tree for MRM Testing"
Attachment 2: International Residue Limit Status Sheet

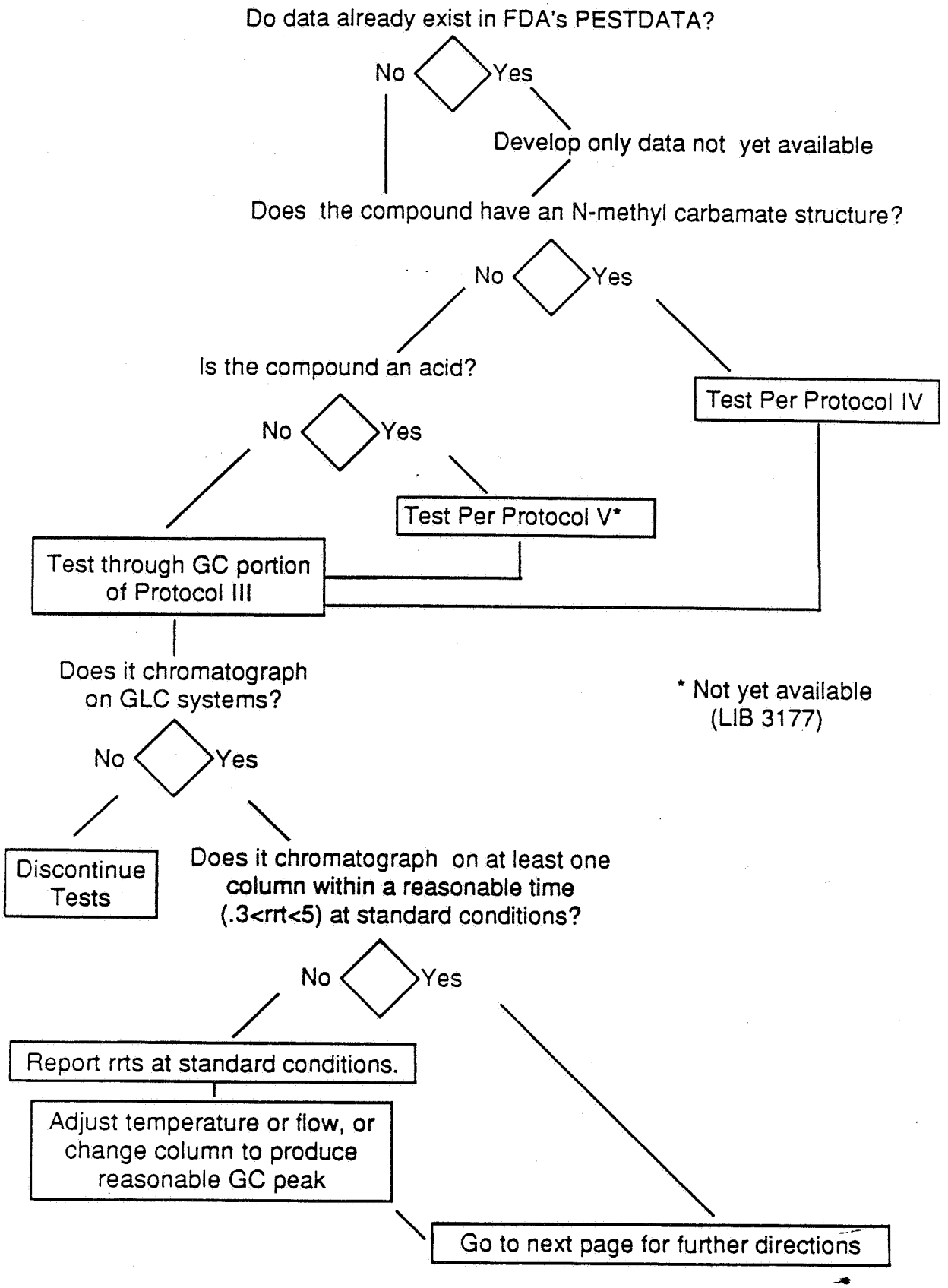
cc: RF, Circu., PP#8F3673, ISB/PMSD (Eldredge), Reviewer (Mike Flood)

RDI:Section Head:RSQuick:1/31/89:Deputy Chief:RDSchmitt: 1/31/89.
TS-769C:DEB:557-4362:MTF;mtf:CM#2:RM810:2/1/89.
53353:I/WP:Flood:C.Disk:KENCO:01/25/89:DD:VO:DD:EK:DD

(19)

Decision Tree for MRM Testing

DRAFT



* Not yet available (LIB 3177)

FDA Division of Contaminants Chemistry
revised May,1988

(20)

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Glyphosate

CODEX NO. 155

CODEX STATUS:

[/] No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Crop(s)	Limit (mg/kg)
Wheat	0.05

PROPOSED U.S. TOLERANCES:

Petition No. PP#8F3673

RCB Reviewer MIKE FLOOD

Residue: Glyphosate and N-anunomethylphosphonic acid (AMPA)

Crop(s)	Limit (mg/kg)
CORN:	
GRAIN	1 ppm
FODDER	30 ppm
FORAGE	20 ppm

CANADIAN LIMITS:

[/] No Canadian limit

Residue: _____

Crop(s)	Limit (mg/kg)
	1

MEXICAN LIMITS:

[/] No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES:

Form revised 1986