

Glyphosate Registration Standard File

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

SEP 25 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration Nos. 524-318, -333, and -339 Glyphosate.
Comparison of Analytical Methods and Response to
Registration Standard.
(Accession Nos. 265985 and 262896)
[RCB Nos. 2372, 2373, and 2374]

FROM: Francis D. Griffith, Jr., Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

A handwritten signature in cursive script, reading "Francis D. Griffith, Jr.", written over the typed name and title.

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

and

Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Robert S. Quick, Section Head, TPS-I
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

Handwritten initials "RMP" in a stylized, bold font.

By letter dated October 14, 1986, Monsanto Company, registrant of products containing glyphosate as the active ingredient, has submitted reports to comply with the Registration Standard issued August 11, 1986. Monsanto requests the Agency review the comparison of analytical methods for residues of glyphosate in various commodities and make the newer "faster" HPLC-fluorescence method available to FDA for publication in PAM-II. The Glyphosate Guidance Document (Table A) indicates the HPLC method has completed a successful method tryout (MTO) and should be published in PAM II. The registrant also has a newer version HPLC-fluorescence glyphosate residue method and now requests the newer version be published in PAM-II as well. This new method is undergoing a MTO.

In this package, submitted to RCB for review, were reports RD No. 677 (MSL-5677) titled "Validation of New Residue Method and Reanalysis of Glyphosate Residues in Water," dated May 19,

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1986; RD No. 707, titled "Information to Support the Registration of Roundup® Herbicide," dated October 20, 1986; and RD No. 710, titled "Comments to Glyphosate Guidance Document," dated November 7, 1986.

Discussion

Product Chemistry

In the report "Comments to Glyphosate Guidance Document," the registrant has completed FIFRA section 3(c)(2)(B) Summary Sheets for Roundup® Herbicide, Rodeo® Herbicide, Roundup® L&G Herbicide, Shackle® Herbicide, Shackle® C Herbicide, Polado® Plant Growth Regulator, Mon-0139 technical solution (53.5%), CP-70139 Herbicide, Mon-0139 62% solution, Bronco® Herbicide, Landmaster® Herbicide, Landmaster® II Herbicide, and Ranger® Herbicide. The company has agreed to submit the required data in a timely manner. The registrant has submitted new Confidential Statements of Formula (CSFs) for each of these products. Review of the CSFs for these products is now the purview of Registration Division (RD).

Comments on the chronic mouse study, environment fate studies, and worker safety rules are not germane to Residue Chemistry Branch (RCB) and will not be commented on in this review. The PM should forward these to the appropriate Hazard Evaluation Division (HED) branches for review and comment.

In comments on Table A, Generic Data Requirements for Glyphosate, section 158.120--Product Chemistry, the petitioner claims to have submitted data to satisfy the deficiency. Product Chemistry data were reviewed as part of an amendment to PP#6F3380/6H5502 (q.v. memorandums by W.T. Chin dated July 6, 1987, and J. Stokes September 1, 1987). The product manager is referred to these reviews.

Residue Chemistry

For the Residue Chemistry Data Requirements under §158.125, the registrant agrees on page 35 of the Comments document to conduct the requested animal metabolism studies and generate the field trial residue data to support the existing tolerances. The exception is for the stone fruits group. For stone fruits, the petitioner requests a 17-day PHI and plans no processing study for plums. Since the petitioner has agreed to do a grape processing study, and since the processing of both grapes and plums is essentially only a drydown procedure, RCB defers judgment on the plum processing study requirement until we have received and reviewed the grape processing study.

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In the section on detailed comments for the plant metabolite (page 12, paragraph 4), RCB notes the metabolite AMPA is in the tolerance expression. The petitioner argues that the levels are generally in the ppb range, AMPA degrades rapidly, and its exposure to humans either from water or plants would be quite low. This section is more germane to Toxicology Branch decision than RCB. RCB requests TB decide whether or not further information is needed, particularly on residues of AMPA in soybeans.

In paragraph d, page 19, residue data, the registrant requests RCB add the words "and enforcement" to the end of the last sentence. RCB has received complaints over length of time needed to run this method from several States as well as FDA enforcement labs. The method as written cannot meet the Residue Chemistry Guidelines criterion of 1-day turnaround. At present, we have a newer HPLC-fluorescence method undergoing a MTO in which the registrant claims 1 day turnaround. If the method passes the MTO it will become the prime enforcement procedure. RCB thus declines to add "and enforcement" to this sentence.

Labeling

Various label restrictions have been proposed. RCB previously has prohibited the use of glyphosate on rice fields in which catfish or crayfish are double-cropped.

The petitioner points out there is a 0.25 ppm glyphosate tolerance for fish. This includes catfish, thus that part of the restriction no longer applies. While RCB has recommended for the proposed glyphosate in shellfish tolerance, it has not yet been established. Until the glyphosate in shellfish tolerance is established, the label restriction on glyphosate in rice fields double-cropped with crayfish should remain intact.

RCB accepts Monsanto's proposed feeding and grazing restriction for pineapple and sugarcane forage. We also accept the revised labels for cancellation of specific 24(c) registrations on sorghum/selective equipment. Monsanto also agrees to make various changes in the tolerance listings as suggested by the Agency.

Irrigation Crops

The Agency has established a number of crop group tolerances at 0.1 ppm from irrigation waters containing 0.5 ppm glyphosate. As long as the use of irrigation water, including water from rice fields, containing 0.5 ppm glyphosate to the crop groups and individual commodities are listed on the label then RCB agrees further label restrictions are not needed for those crops.

To retain glyphosate tolerances from irrigation uses, the Agency requested additional field trial data. The registrant responded that a previous report showing irrigation waters containing 0.5X and 5X application rates for 3 consecutive days on the following representative commodities and their crop groups:

- 1) alfalfa of the non-grass animals feeds (forage, fodder, straw and hay) group,
- 2) field beans of the legume vegetables (succulent or dried) group,
- 3) sorghum of the cereal grains group,
- 4) sorghum fodder of the forage, fodder, and straw of the cereal grains group,
- 5) squash of the cucurbits vegetables group,
- 6) sugarbeets of the root and tuber vegetables group,
- 7) tomatoes of the fruiting vegetables (except cucurbits) group.

Only sorghum fodder contained high residues above tolerance, 1.8X from the 5X application. Other residues were all non-detected. All of these crops are major commodities whether used as human or animal foods. Since the study involved 3 days of irrigation at a constant 5X level, a situation that we would not expect to be found in the real world, RCB considers this is a worst case scenario. Thus additional field trial data are not necessary to support these crop groupings. We agree additional field trial data will not be required for crop group tolerances for the proposed irrigation uses. However, the other part of item 17 on page 26 still stands, namely the petitioner needs to propose a complete revision of 40 CFR 180.364(c). The presently listed crop groupings should be deleted and new listings proposed that are consistent with the nomenclature used in 40 CFR 180.34(f) (I through XVIII, excluding the herbs and spices crop group, XIX). Since RCB has no previous residue field trial data for commodities listed in crop group XIX and for the crops not in a crop group such as those in 180.34(f)(7); i.e., banana, peanuts, mushrooms, etc., the Agency will require field trial glyphosate residue data from the proposed use to support a 40 CFR 180.364(c) tolerance.

Method Comparisons

The document RD No. 677, titled "Validation of New Residue Method and Reanalysis of Glyphosate Residues in Water"

has been previously submitted to RCB as part of PP#6F3380/6H5502 and reviewed in a memorandum by W.T. Chin dated July 6, 1987. This review lead to the MTO request by J. Stokes on July 7, 1986, to COB/BUD for validation of the method on soybeans, apples, and wheat. After further consideration, RCB has these comments. Recovery data on proposed enforcement methods that are less than 70 percent make the method questionable. Any time recoveries are at the 20 to 25 percent and/or 130+ percent level, RCB has grave concerns over the ability of the method of function as proposed. From the body of recovery data presented, the highs and lows in recovery may reflect a normal distribution; however, RCB will be attuned to enforcement lab comments on the new method. Since this method is consistently giving higher recoveries of glyphosate, up to 50 percent better in some instances, RCB expects to see an increase in glyphosate incident reporting for the shorter method. We point out the potential for more positive samples and results closer to existing tolerances will be expected, but we lack data to show the established tolerances will be exceeded, thus revised tolerances are not in order at this time.

The new method utilizes a Sorval® 2C2B refrigerated high speed centrifuge (or equivalent) run at 11,000 rpms for 20 minutes. This type of equipment is not listed in PAM-I as a standard item for residue analysis. For major/large State laboratories and FDA regional labs access to a high speed, refrigerated centrifuge in the microbiology sections is possible, thus we raise no issue at this time.

Reviewing the selected chromatograms and raw data presented for the analysis of water by the two methods, RCB concludes the limit of sensitivity or quantification for the new method (HPLC) is 5 ppb while the limit of detection is 0.5 ppb.

The fourth document submitted for review, coded RD No. 707, shows comparative results from the present GLC method and a version of the proposed HPLC method for water, cottonseed, soybeans, pasture grasses, and alfalfa. The versions of the HPLC method used in this report are the ion exchange column Chelex® 100 resin in the Fe (III) form, an Aminex A9, 10 cm x 4.6 mm (id) HPLC column, and a ninhydrin post column reaction with an absorbance detector (546 nm filter) for analysis of water, soybeans, cottonseed, grasses, and alfalfa. The direct analysis of water version of the method used the post column OPA/fluorescence detector and the same column as above. The method undergoing an MTO uses the Chelex® 100 resin in FE (III) form, an Aminex A9, 30 cm x 4.6 mm (id) HPLC column and an OPA post column reaction with a fluorescence detector. RCB considers that ninhydrin/absorbance and OPA/fluorescence give comparable results without an MTO. A 10 cm vs. a 30 cm HPLC

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column only enhances separation of the analytes of interest from potential unidentified analytical responses (UARS). While run times are longer with a 30 cm column this is not considered a problem when using an automated liquid sampler (ALS) such as the Varian 8500 or Waters WISP 710A. Comparisons of recoveries continue to show the Chelex®/HPLC method regardless of which of the post column reactions/detectors gives consistently higher recoveries with smaller standard deviations (and smaller coefficient of variation).

The petitioner presented comparison analyses of results for 81 samples run by GLC vs. HPLC, and another 25 results of direct analyses by HPLC vs. GLC in water for a total of 106 samples. Water samples consistently showed higher results by HPLC; 28 out of 37 samples were higher glyphosate by HPLC while only 1 out of 37 have higher glyphosate residues by GC. Samples of flowing water showed the maximum instantaneous residues of glyphosate were higher than the established tolerance. Downstream dissipation of glyphosate residues occurs rapidly due to dilution to levels less than the 0.5 ppm. RCB expects more positive samples closer to the tolerance, however, the water tolerances do not need revision at this time.

Reanalysis of computer-selected samples of soybeans, cottonseed, and pasture grasses shows more than half of 34 samples had comparable results from GLC or HPLC analysis; 10 out of 34 samples showed higher glyphosate residue by HPLC and 5 out of 34 samples had slightly higher glyphosate residues by GLC. The ratio of GLC to HPLC results ranged generally from 0.5 to 2 with no additional samples being over tolerance. For example, the glyphosate residues in the grass sample from Kennesaw, GA show glyphosate by GLC at 2.6 ppm but at 78.9 ppm by HPLC. This reinforces our comment that there will be more higher--but not necessarily overtolerance--glyphosate residues. At or just above the limit of quantification/sensitivity, the HPLC and GLC methods gave more nearly comparable results regardless of the matrix. At higher levels, HPLC seems to give higher results. The petitioner's hypothesis is that there is incomplete derivatization. RCB feels this may be the problem in some samples but also only part of the time. Since the correlation is not strong and direct with increasing concentration, other reasons such as matrix effects need more consideration.

RCB reiterates the HPLC glyphosate method is an improvement over the GLC method. It generally gives equal or higher, and more consistent recoveries. To aid the States in their monitoring and enforcement efforts whether in water or food samples RCB recommends the petitioner provide clean, non-CBI or proprietary (no copyright) methods using the ninhydrin/absorbance detector to enforce food tolerances, and the

direct injection HPLC version to enforce the 0.5 ppm water tolerance in 40 CFR 180.364(c). RCB concludes these versions of the method should be published in PAM-II if and when the Chelex®/HPLC/OPA-fluorescence method passes the MTO.

RCB Conclusions

1. The registrant has submitted the appropriate FIFRA 3(c)(2)(B) Summary Sheets indicating data will be submitted, new CSFs, and comparison of methods. The review of CSF data is now under the purview of RD.
2. The chronic mouse study, environmental fate studies, and the worker safety study will not be reviewed by RCB as these studies are germane to other HED branches.
- 3a. The petitioner has agreed to provide additional field trial data to support glyphosate tolerances, except for a plum processing study. RCB defers judgment on the acceptability of this until we have received and reviewed the grape processing study.
- 3b. The petitioner has agreed to provide results of glyphosate metabolism studies in ruminants and poultry.
- 4a. In labeling, RCB agrees a label restriction for catfish farming in rice fields is not necessary as there is a 0.25 ppm glyphosate in fish tolerance. However, until the shellfish glyphosate tolerance is established, the restriction on double-cropping crayfish in rice fields must remain.
- 4b. RCB accepts the proposed revised labeling for cancellation of specific 24(c) registrations on sorghum/selective equipment and imposing a grazing and feeding restriction for pineapple and sugarcane forage.
- 4c. The registrant needs to completely revise 40 CFR 180.364(c) by deleting the existing crop groupings and propose new groupings that are consistent with the nomenclature used in 40 CFR 180.364(f) (I thru XVIII, excluding the herbs and spices crop group, XIX). Since RCB does not have field trial residue data for commodities in the herbs and spices crop group, XIX, and for other commodities not listed in a crop group, additional field trial data are required for crop group XIX and for the non-crop group commodities. However the petitioner has

provided 5X data for representative commodities in seven crop groupings, thus additional data from the proposed irrigation use to support tolerances on crop groups I through XVIII for 180.364(c) are not required.

- 4d. RCB requests TB decide whether or not further information is needed on the plant metabolite AMPA particularly in soybeans. The petitioner's discussion on the plant residues of AMPA is more germane to TB decisions than RCB.
- 5a. The petitioner has presented comparison results from the new HPLC method and the present GLC method to show both methods provide satisfactory results.
- 5b. The HPLC method in general gives equal or higher, and more consistent recoveries.
- 5c. With the new Chelex® HPLC, OPA/fluorescence method RCB points out the potential for more positive glyphosate samples and results closer to existing tolerances. Overall data are lacking to show tolerances need to be revised upward.
- 5d. RCB points out a high speed refrigerated centrifuge (11,000 rpm, 20 minutes) is not a standard piece of equipment in most residue labs. At this time this should not be a problem for large State and regional FDA labs that also have microbiology sections.
- 5e. The limit of sensitivity or quantification should be stated as 5 ppb in water and the water limit of detection should be 0.5 ppb.
- 5f. The petitioner needs to provide clean non-CBI, nonproprietary (no copyright) methods that use ninhydrin post column reaction and absorbance detection to enforce the glyphosate tolerances in foods, and the direct injection HPLC version of the method to enforce/monitoring the 0.5 ppm water tolerance. RCB needs these methods for publication in PAM-II at the same time we publish the present MTO method assuming it passes the MTO. These comparison methods are an aid to State monitoring and enforcement of glyphosate residues and tolerances.

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RCB Recommendation

RCB recommends this review be forwarded to the registrant for his responses to Conclusions 3, 4, and 5. The Product Manager needs to respond to Conclusions 1 and 2.

TS-769C:RCB:Reviewer (FDG):CM#2:814B:557-0826:KENCO:JOB:92062:C.Disk
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cc: R.F., Circu, Glyphosate Registration Standard File,
Reviewer, PM 25, ISB/PMSD.
RDI:Section Head:R.S. Quick:9/24/87:R.D. Schmitt:9/24/87.