



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

Kramer

JUL 31 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP# 5F04493. Glyphosate in or on Cotton. Evaluation of Residue Data and Analytical Methods. MRID# 435718. [01] Barcodes D214931 & D214929. CBTS#s 15546 & 15547.

FROM: G.F. Kramer, Ph.D., Chemist
Tolerance Petition Section III *G.F. Kramer*
Chemistry Branch I, Tolerance Support
Health Effects Division (7509C)

THRU: M.S. Metzger, Branch Chief
Chemistry Branch I, Tolerance Support *Metzger*
Health Effects Division (7509C) *M.S. Metzger*

TO: Robert Taylor, Product Manager
Vickie Walters, Team 25 Reviewer
Registration Division (7505C)

And

Jane Smith, Acting Section Head
Registration Section, RCAB
Health Effects Division (7509C)

Monsanto has submitted a petition for tolerances for residues of the herbicide glyphosate (N-(phosphonomethyl)glycine) in/on cotton gin byproducts. This tolerance is requested in conjunction with an application for registration of Roundup Herbicide for use on genetically engineered cotton (Roundup-Ready Cotton). Tolerances, expressed as the parent plus the metabolite AMPA (aminomethyl phosphonic acid), are currently established for numerous commodities under 40 CFR § 180.363(a) including cottonseed at 15 ppm. The proposed tolerance is:

Cotton gin byproducts -- 100 ppm

PC 103601

MRID 43571801



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Executive Summary of Chemistry Deficiencies

- Revise label.

or

- Additional field trial data.

BACKGROUND

Glyphosate controls weeds through inhibition of 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSSPS), an enzyme in the aromatic amino acid biosynthetic pathway. Monsanto has genetically modified cotton to express agrobacterium EPSSPS which is resistant to glyphosate. Cotton expressing this gene can tolerate glyphosate at rates up to 2.25 lbs. ai/A per application.

CONCLUSIONS

1. The maximum use rate for the post-directed application is 0.75 lbs. ai. No unit of area is specified. The use rate must thus be revised; i.e. 0.75 lbs. ai/A. **A revised Section B is required.**
- 2a. A total of 11 field residue trials were conducted in 1994 in eight different states, which together accounted for 86% of the U.S. cotton acreage in 1991 (*Agricultural Statistics*, 1992). Three different treatment regimens were employed in separate plots at each site. Analysis of the treated samples showed that the maximum glyphosate residue in cotton gin byproducts was 88.7 ppm and in cottonseed was 6.4 ppm.
- 2b. The registrant has submitted a total of 10 acceptable cotton residue trials. One trial is unacceptable as the PHI (17 days) differed significantly from the minimum PHI (7 days). The distribution does not correspond with that suggested for cotton in *EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances*, 6/2/94. However, as the states in which these trials were performed represented 80% of U.S. Cotton acreage in 1991 (*Agricultural Statistics*, 1992) and at least three separate plots were included in each trial, CBTS concludes that the number of trials and the geographic representation are adequate to establish tolerances for glyphosate in cotton gin byproducts.
- 2c. However, the field trial data do not reflect the proposed use on Roundup-Ready cotton or the established use on normal cotton.

i) The use rate employed for the preharvest application was only 0.4X of the maximum use rate permitted for this application. The registrant must provide residue data for cotton gin byproducts from trials which include a 1X preharvest application or change the labelling for cotton (both normal and modified) to specify that the maximum use rate for the preharvest application is 1.5 lbs. ai/A.

ii) Directions for the use of adjuvants (nonionic surfactants and ammonium sulfate) are contained on the Roundup labels but the use of these compounds was not represented in the preharvest application of any trial. The registrant must provide residue data for cotton gin byproducts from trials which include a preharvest application utilizing nonionic surfactants and ammonium sulfate or change the labelling for cotton (both normal and modified) to specify that the use of additives for the preharvest application is not permitted. The use of additives in the other applications is not likely to influence the potential for residues in cottonseed and cotton gin byproducts as the vast majority of the residues will result from the preharvest application. If the former option is chosen, CBTS would have no objection to a time-limited tolerance with conditional registration while the required bridging data are generated.

2d. If the directions for use are modified as recommended above, then the submitted residue data will support the proposed tolerance for residues of glyphosate on cotton gin byproducts of 100 ppm.

3. Cottonseed from the TX trial (Treatment 2) was processed into delinted seed, hulls, kernels, meal, crude oil, refined oil bleached-deodorized refined oil and soapstock. Glyphosate residues do not appear to concentrate in processed commodities. Feed/feed additive tolerances are thus not required for this petition.

4. HED has recommended that a tolerance of 100 ppm be established for residues of glyphosate on the non-grass animal feeds group. As members of this group (i.e., alfalfa) are more significant animal feed items than cotton gin byproducts, the establishment of a tolerance of 100 ppm on cotton gin byproducts will not increase the theoretical maximum dietary exposure. Therefore, a DRES run is not required for this tolerance.

5. There is no Codex proposal, nor Canadian or Mexican limits for residues of glyphosate on cotton gin byproducts. Therefore, a compatibility issue is not relevant to the proposed tolerance. A copy of the IRLS sheet is attached to this memorandum.

6. Rotational crops were the subject of a recent meeting and will be discussed in a separate review.

RECOMMENDATIONS

CBTS recommends against the proposed tolerance for glyphosate on cotton gin byproducts for reasons detailed in conclusions 1 and 2c.

DETAILED CONSIDERATIONS

Product Chemistry

No new studies were submitted with this petition. Any deficiencies in product chemistry will be addressed through reregistration.

Formulation

Glyphosate is formulated as Roundup Herbicide (EPA Reg. No. 524-445), a soluble concentrate containing 41% a.i. (3 lbs. ai/gal) and Roundup D-Pak Herbicide (EPA Reg. No. 524-333) a soluble concentrate containing 62% a.i. (4.75 lbs. ai/gal). The registrant has proposed to revise the labels for both formulations. However, as both products are soluble concentrates, residue data will not be required for each formulation.

Proposed Use

The following uses are specific to Roundup Ready cotton: **Over-the-top-** Roundup may be applied postemergent until the pinhead square stage. The maximum use rate is 0.75 lbs. ai/A. A maximum of two applications may be performed, with a minimum retreatment interval of 10 days. **Post-directed-** Roundup may be applied by a directed or hooded sprayer until layby. The maximum use rate is 0.75 lbs. ai. No unit of area is specified. A maximum of two applications may be performed, with a minimum retreatment interval of 10 days. For both treatment types, the spray volume is 3-15 gal/acre by ground and 3-10 gal/acre by air. Non-ionic surfactants (0.5%) or ammonium sulfate (2%) may be added to the finished spray.

In addition to these uses, the standard preplant and preharvest applications may also be performed. The maximum application rate is 1.5 lbs. ai/A for annual weeds and 3.75 lbs. ai/A for perennial weeds. The total seasonal maximal application rate is 10.5 lbs. ai/A. The PHI is 7 days.

The following deficiency in the label was noted: The maximum use rate for the post-directed application is 0.75 lbs. ai. No units of

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area is specified. The use rate must thus be revised; i.e. 0.75 lbs. ai/A. A revised Section B is required.

Nature of Residue- Plants and Animals

The HED Metabolism Committee has decided that only glyphosate per se is of regulatory concern and that AMPA is not of toxicological concern regardless of its level in food (Memo, R. Perfetti 3/17/94).

Analytical Methodology- Plants

Adequate enforcement methods are available for analysis of residues of glyphosate in or on plant commodities. These methods include GLC (Method I in *Pesticides Analytical Manual (PAM) II*; the limit of detection is 0.05 ppm) and HPLC with fluorometric detection. Use of the GLC method is being discouraged due to lengthiness of the procedure. The HPLC method has undergone successful Agency validation and was recommended for inclusion in *PAM II*; the limit of detection is 0.0005 ppm. A GC/MS method for glyphosate in crops has also been validated by ACL (Memo, G. Kramer 3/21/95). This method has not yet been submitted for publication in *PAM-II*.

Storage Stability Studies

No storage stability data were submitted with this petition.

The samples from the field residue and processing studies were stored for a maximum of 5 months. Glyphosate residues have been shown to be stable in a variety of crop matrices for up to 2.5 years of frozen storage at -18 °C (Memo, C. Eiden 11/17/94). Storage stability is thus not an issue for this petition.

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Magnitude of Residue- Plants

Submitted with this petition:

Magnitude of the Residues in Glyphosate-Tolerant Cotton Raw Agricultural and Processed Commodities. MRID# 435718-01

A total of 11 field residue trials were conducted in 1994 in eight different states, which together accounted for 86% of the U.S. cotton acreage in 1991 (Agricultural Statistics, 1992). These trials were located in Regions 2 (1 trial), 4 (5 trials), 6 (2 trials), 8 (1 trial) and 10 (2 trials). Three different treatment regimens were employed in separate plots at each site. Treatment 1 consisted of a preemergent application at a rate of 3.0 lbs. ai/A (0.8X), a postemergent application at a rate of 1.125 lbs. ai/A (3-4 leaf stage) (0.75X), a post-directed application at a rate of 1.125 lbs. ai/A (0.75X) and a preharvest application at a rate of 1.5 lbs. ai/A (0.4X). Treatment 2 consisted of a preemergent application at a rate of 3.0 (0.8X) lbs. ai/A, a postemergent application at a rate of 0.75 lbs. ai/A (3-4 leaf stage), a postemergent application at a rate of 1.125 lbs. ai/A (5-6 leaf stage) (1.25X of the total postemergent rate), a post-directed application at a rate of 1.125 lbs. ai/A (0.75X) and a preharvest application at a rate of 1.5 lbs. ai/A (0.4X). Treatment 3 consisted of a preemergent application at a rate of 3.0 lbs. ai/A (0.8X), a postemergent application at a rate of 0.75 lbs. ai/A (3-4 leaf stage), a postemergent application at a rate of 1.125 lbs. ai/A (7-8 leaf stage) (1.25X of the total postemergent rate), a post-directed application at a rate of 1.5 lbs. ai/A (1X) and a preharvest application at a rate of 1.5 lbs. ai/A (0.4X). Two different lines of genetically modified cotton were evaluated independently at five sites (i.e., three plots of each type). The spray volume was 9-21 gal/A. Roundup Herbicide was used in all trials. Samples were harvested from each treated plot 6-17 days after the preharvest application. Cotton gin byproducts samples in two trials (AR, TN) were obtained by collecting material from the gin. In the other trials, cotton gin byproducts samples were simulated by collecting leaves, burrs, stems and lint from the field. Samples were analyzed for glyphosate and AMPA using the HPLC-fluorometric method previously reviewed by CBTS (Memo, R. Cook 1/29/91). The method was validated in cotton seed over a range of 0.06-50.0 ppm and in cotton gin byproducts over a range of 0.03-100.0 ppm. The average recovery in cottonseed was 86.3% for glyphosate and 87.3% for AMPA. The average recovery in cotton gin byproducts was 84.6% for glyphosate and 82.6% for AMPA. Analysis of the treated samples showed that the maximum glyphosate residue in cotton gin byproducts was 88.7 ppm (Table 1) and in cottonseed was 6.4 ppm (Table 2).

Table 1- Glyphosate and AMPA residues in cotton gin byproducts. See above discussion for details of each treatment.

Location	Treatment #	Spray Volume (gal/A)	PHI (Days)	Maximum Residues (ppm)	
				Glyphosate	AMPA
AL	1	20.8	7	10.8	0.1
	2	20.8	7	8.8	0.1
	3	20.8	7	17.2	0.2
AR	1	12.9	8	4.4	0.1
	2	12.6	8	7.9	0.1
	3	12.8	8	9.0	0.1
AZ	1	18.6	7	43.3	0.3
	2	18.6	7	23.7	0.2
	3	18.6	7	34.0	0.2
CA	1	14.6	6	39.1	0.4
	2	14.3	6	28.7	0.3
	3	14.3	6	20.9	0.2
LA	1	10.2	17	2.4	0.04
	2	10.1	17	2.0	0.03
	3	10.1	17	1.0	0.02
MS	1	15.5	6	31.8	0.3
	2	15.5	6	33.7	0.3
	3	15.5	6	30.3	0.1
MS	1	14.3	9	6.2	0.1
	2	14.3	9	4.6	0.05
	3	14.3	9	5.7	0.05
TN	1	12.9	8	33.9	0.5
	2	12.8	8	27.7	0.3
	3	13.0	8	29.3	0.3
TX	1	12.1	6	32.6	0.3
	2	12.1	6	88.7	0.9
	3	12.1	6	78.5	0.7
TX	1	19.8	8	18.5	0.2
	2	20.1	8	21.9	0.3
	3	20.1	8	19.6	0.2
TX	1	19.9	7	29.5	0.1
	2	15.0	7	43.4	0.3
	3	15.0	7	32.0	0.2

Spray volume of preharvest application

Table 2- Glyphosate and AMPA residues in cottonseed. See above discussion for details of each treatment.

Location	Treatment #	Spray Volume (gal/A)	PHI (Days)	Maximum Residues (ppm)	
				Glyphosate	AMPA
AL	1	20.8	7	0.52	0.00
	2	20.8	7	0.55	0.03
	3	20.8	7	0.48	0.04
AR	1	12.9	8	0.75	0.22
	2	12.6	8	0.79	0.12
	3	12.8	8	0.76	0.02
AZ	1	18.6	7	1.51	0.12
	2	18.6	7	0.49	0.00
	3	18.6	7	1.11	0.03
CA	1	14.6	6	2.96	0.08
	2	14.3	6	2.29	0.07
	3	14.3	6	1.54	0.08
LA	1	10.2	17	0.70	0.04
	2	10.1	17	0.65	0.05
	3	10.1	17	0.43	0.04
MS	1	15.5	6	4.90	0.08
	2	15.5	6	5.03	0.10
	3	15.5	6	0.94	0.00
MS	1	14.3	9	1.28	0.08
	2	14.3	9	0.99	0.04
	3	14.3	9	0.63	0.04
TN	1	12.9	8	3.05	0.11
	2	12.8	8	6.40	0.15
	3	13.0	8	5.24	0.08
TX	1	12.1	6	2.54	0.05
	2	12.1	6	2.36	0.03
	3	12.1	6	2.61	0.05
TX	1	19.8	8	4.17	0.14
	2	20.1	8	4.56	0.15
	3	20.1	8	4.38	0.15
TX	1	19.9	7	1.90	0.00
	2	15.0	7	2.87	0.01
	3	15.0	7	5.40	0.06

*Spray volume of preharvest application

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Conclusions: The registrant has submitted a total of 10 acceptable cotton residue trials. The LA trial is unacceptable as the PHI (17 days) differed significantly from the minimum PHI (7 days). These trials were located in Regions 2 (1 trial), 4 (4 trials), 6 (2 trials), 8 (1 trial) and 10 (2 trials). This distribution does not correspond with that suggested for cotton in *EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances*, 6/2/94: Regions 2 (1 trial), 4 (3 trials), 6 (1 trial), 8 (4 trials) and 10 (3 trials). However, as the states in which these trials were performed represented 80% of U.S. Cotton acreage in 1991 (*Agricultural Statistics*, 1992) and at least three separate plots were included in each trial, CBTS concludes that the number of trials and the geographic representation are adequate to establish tolerances for glyphosate in cotton gin byproducts. However, the field trial data do not reflect the proposed use on Roundup-Ready cotton or the established use on normal cotton:

1) The use rate employed for the preharvest application was only 0.4X of the maximum use rate permitted for this application. The registrant must provide residue data for cotton gin byproducts from trials which include a 1X preharvest application or change the labelling for cotton (both normal and modified) to specify that the maximum use rate for the preharvest application is 1.5 lbs. ai/A.

2) Directions for the use of adjuvants (nonionic surfactants and ammonium sulfate) are contained on the Roundup labels but the use of these compounds was not represented in the preharvest application of any trial. The registrant must provide residue data for cotton gin byproducts from trials which include a preharvest application utilizing nonionic surfactants and ammonium sulfate or change the labelling for cotton (both normal and modified) to specify that the use of additives for the preharvest application is not permitted. The use of additives in the other applications is not likely to influence the potential for residues in cottonseed and cotton gin byproducts as the vast majority of the residues will result from the preharvest application. If the former option is chosen, CBTS would have no objection to a time-limited tolerance with conditional registration while the required bridging data are generated.

If the directions for use are modified as recommended above, then the submitted residue data will support the proposed tolerance for residues of glyphosate on cotton gin byproducts of 100 ppm.

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Magnitude of the Residue- Processed Fractions

Cottonseed from the TX trial (Treatment 2) was processed into delinted seed, hulls, kernels, meal, crude oil, refined oil bleached-deodorized refined oil and soapstock. Glyphosate residues do not appear to concentrate in processed commodities (Table 3). Feed/feed additive tolerances are thus not required for this petition.

Table 3- Residue data for glyphosate sodium in processed fractions of cotton.

Fraction	Residue (ppm)	Concentration Factor
Cottonseed RAC	3.67	-
Delinted Seed	0.63	0.17
Kernels	0.24	0.07
Hulls	1.22	0.33
Meal	0.39	0.11
Crude Oil	<0.05	-
Refined Oil	<0.05	-
Bleached-Deodorized Refined Oil	<0.05	-
Soapstock	0.01	0.004

Magnitude of the Residue- Ruminants

No new studies were submitted with this petition.

HED has recommended that a tolerance of 100 ppm be established for residues of glyphosate on the non-grass animal feeds group. As members of this group (i.e., alfalfa) are more significant animal feed items than cotton gin byproducts, the establishment of a tolerance of 100 ppm on cotton gin byproducts will not increase the theoretical maximum dietary exposure. Therefore, a DRES run is not required for this tolerance.

Other Considerations:

There is no Codex proposal, nor Canadian or Mexican limits for residues of glyphosate on cotton gin byproducts. Therefore, a compatibility issue is not relevant to the proposed tolerance. A copy of the IRLS sheet is attached to this memorandum.

Rotational crops were the subject of a recent meeting and will be discussed in a separate review.

Attachment- IRLS Sheet

cc: PP#5F04493, Kramer, R.F., circ.
RDI: F.D. Griffith (7/19/95), M.S. Metzger (7/28/95), M.J. Nelson
for R.A. Loranger (7/27/95)
G.F. Kramer: 804T: CM#2: (703) 305-5079, 7509C



Attachment:

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INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL glyphosate

CODEX NO. 158

CODEX STATUS:

☒ No Codex Proposal
Step 6 or Above (on gin byproducts)*

Residue (if Step 8): _____

PROPOSED U.S. TOLERANCES:

Petition No. 5F04493

CBTS Reviewer G.F. Kramer

Residue: _____

Crop(s) Limit
 (mg/KG)

Crop(s) Limit
 (mg/KG)

Cotton Gin Byproducts- 100

CANADIAN LIMITS:

☒ No Canadian Limits (on gin byproducts)

Residue: glyphosate

Crop(s) Limit
 (mg/KG)

MEXICAN LIMITS:

☒ No Mexican Limits

Residue: _____

Crop(s) Limit
 (mg/KG)

NOTES

*N-(phosphonomethyl)glycine

* There is a Codex limit on cottonseed (0.5 ppm)

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