

4-18-85



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

APR 18 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Accession No. 073100. [RCB No. 537, 538]
PP3F2809/FAP5H5450: Glyphosate in or on Wheat Grain and
Wheat Straw. Amended Section F and D, letter of 11/13/84
and new Food Additive Petition.

TO: R. Taylor, PM 25
Registration Division (TS-767)
and
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

FROM: R. W. Cook, Chemist *R.W. Cook*
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

In the previous submission for subject petition, Monsanto Co. proposed tolerance at 0.2 ppm for combined residues of the herbicide glyphosate (N-phosphonomethylglycine) and its metabolite aminomethylphosphonic acid in wheat grain. Now, Monsanto Co. proposes tolerances for combined residues as above in or on wheat grain at 0.25 ppm and 0.35 ppm in wheat straw and food additive tolerances are proposed for combined residues of glyphosate at 0.4 ppm in wheat bran and 0.3 ppm in wheat shorts. A cover letter submitted in conjunction with the amendment states the proposed tolerances are 0.2 ppm for grain and 0.3 ppm for straw. While we have requested the petitioner to clarify this situation, we must consider the submitted Section F prevailing. (Telecon: L. Gingerich, Monsanto, and R. W. Cook, RCB).

Tolerances are currently established in 40 CFR 180.364 for combined residues of glyphosate and aminomethylphosphonic acid at levels of 0.1 ppm (N) in grain crops and 0.2 ppm in forage grasses. Glyphosate is currently undergoing review in the Registration Standard process.

Several deficiencies were noted in our previous review (R. B. Perfetti, 4/1/83). We shall repeat the deficiency, provide the petitioner's response, and finally, give our comments or conclusions on the response.

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Deficiency #1:

The residue data submitted is not adequate for determination of acceptable tolerance levels in wheat grain, forage, straw and milling fractions. Additional residue data reflecting adequate geographical representation, treatment at the maximum proposed use rate and analysis of grain, forage and straw is needed. A grain milling fraction utilizing wheat containing real residues of glyphosate is also needed to determine whether residues concentrate in any fraction. A revised Section B restricting the grazing of wheat forage will alleviate the need for residue data on this commodity. Appropriate tolerance proposals for the various commodities including food additive tolerances, if any, should be submitted in a revised Section F along with the additional residue and milling studies required.

Our comments/conclusions:

Additional residue data for geographical representation are submitted. Our conclusions are discussed in Residue Data. A grain milling fraction study is discussed in Residue Data: Wheat Milling Study. The revised Section B instructing the user not to ensile wheat forage is not adequate to prevent grazing. Food additive tolerances are proposed for the wheat milling fractions wheat bran and wheat shorts. Our conclusions are found in Residue Data: Wheat Milling Study.

Deficiency #2:

The dairy cattle feeding study (IBT No. 651-3775) employing 10, 30, and 100 ppm of a 3:1 ratio of glyphosate and aminomethylphosphonic acid was an IBT study and was found to be invalid. The only other study on ruminants involved the feeding of 10 ppm of ¹⁴C-labelled glyphosate per se. No tolerances for glyphosate in a cattle feed item could receive a favorable recommendation from RCB until either the existing study is found acceptable or a new study is submitted.

Our comments/conclusions:

We have reviewed the feed palatability study submitted in support of the feeding study IBT No. 651-3775. RCB now considers the Milk and Meat Residue Study with Glyphosate and Aminomethylphosphonic Acid valid (E. Zager, 1/4/85). See discussion under Meat, Milk, Poultry and Eggs below. This deficiency is resolved.

Deficiency #3:

No conclusions with regards to secondary residues of glyphosate in meat, milk, poultry and eggs can be made until both the additional residue data and ruminant feeding studies required above are submitted and reviewed. Depending on the results of the additional residue and milling studies, additional feeding studies may be needed.

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Our comments/conclusions:

The ruminant study has now been validated. See discussion under Meat, Milk, Poultry and Eggs below. This deficiency is resolved.

Conclusions:

1. The metabolism of glyphosate is adequately understood. The residue of concern is glyphosate per se and its metabolite aminomethylphosphonic acid.
2. Adequate analytical methods are available for enforcement of proposed tolerances.
- 3a. The proposed tolerance levels of 0.25 ppm in wheat grain and 0.35 ppm in wheat straw are neither appropriate nor high enough to cover expected residues. We question whether the available data are truly representative of the maximum expected residue levels. We are concerned that ropewick applications appear to be less controllable in regard to amount applied than the usual pesticide application techniques. The condition of the ropewick, drip rate of the ropewick, rate of tractor movement, weed density, and application solution concentration all affect residue levels.

We are unable to draw final conclusions for glyphosate tolerances for wheat grain and wheat straw based upon available residue data. Additional residue data are needed. The petitioner should provide information on the amount or rate of drip of the herbicidal solution onto the crop. The rate of tractor movement should be described, along with some estimate of weed density.

The currently submitted residue data for wiper application of glyphosate on wheat indicate higher glyphosate residues in grain and straw than we would anticipate. The petitioner should discuss any meaningful relationship between conventional dosage rates and selective treatment by wiper application, especially the maximum permitted dosage by wiper. Without definable upper dosage limits, we are concerned that any tolerance which we may establish may not be adequate under some circumstances.

- 3b. The 'hand' application used in the Gretna NE study should be described. In all studies, the plant stage at time of sampling should be identified by such terms as milk stage, dough, or mature grain. The wheat varieties should be identified.
- 3c. The restriction against the use of wheat for ensilage is not adequate to prevent grazing of wheat forage. Residue data for wheat forage receiving wiper applications are needed or a label restriction against grazing of wiper treated wheat forage is needed. The petitioner submits only 4 pages of over 3

100 pages of the total glyphosate label, and we cannot determine whether the previously submitted restriction is still present on the label. The petitioner should be requested to submit a full label.

- 4a. Proposed food additive tolerances of 0.4 ppm in wheat bran and 0.3 ppm in wheat shorts are not appropriate, and the proposed levels are not high enough to cover expected residue levels. Food additive tolerance levels at 3X the level found in the raw agricultural commodity (grain) appear appropriate at this time. A revised Section F expressing food additive tolerances in terms of "Wheat milling fraction (excluding flour)" should be submitted, at the time we are able to draw final conclusions on expected glyphosate residues in wheat grain.
- 4b. TOX has concluded (W. Dykstra, 3/19/85) that food additive tolerances for glyphosate are not appropriate due to the Delaney rule.
5. No residues of glyphosate or its metabolite are likely to occur in meat, fat, meat byproducts (except kidney and liver), milk, or eggs as a result of the use proposed herein. The established kidney and liver tolerances (0.5 ppm) are adequate to cover any secondary residues of glyphosate and its metabolite in kidney and liver of cattle, goats, hogs, horses, poultry, and sheep as a result of the use as proposed.
6. There are no Codex, Canadian, or Mexican tolerances for glyphosate on wheat grain, wheat straw, wheat bran or wheat shorts and we anticipate no problems of compatibility.

Recommendations:

We recommend against the proposed tolerances for the reasons described in Conclusions 3a, 3b, 3c, and 4. For a favorable recommendation the petitioner should address these deficiencies.

Detailed Considerations:

Formulation:

The formulation is Roundup® Herbicide (EPA Reg. No. 524-308) containing 4 pounds per gallon of the isopropylamine salt of glyphosate (equivalent to 3 pounds active ingredient/gallon). All inerts in the formulation are cleared under 40 CFR 180.1001. The manufacturing process has been discussed in our review of PP6G1826.

Directions for Use:

Wiper applications may be used in parsnips, rutabagas, forage grasses and forage legumes including pasture sites and wheat. Allow at least 14 days between application and harvest.

Wheat: Do not use roller applicators.
Do not ensile treated vegetation.

The restriction "Do not ensile treated vegetation" does not prevent grazing and residue data for wheat forage are required.

On page 52 of the glyphosate label submitted 12/17/82 there is the statement, "For other cropping systems do not feed or forage treated crops within 8 weeks after application." Since the petitioner currently submits only a small part (4 pages of over 100 pages) of the total glyphosate label, we cannot determine whether the previously submitted restriction is still present on the label. The petitioner should be requested to submit a full label.

In our previous review, the statement was made that maximum dosage was 6 pounds per acre per year. This statement implied conventional dosage rates. However, a reexamination of this paragraph on the glyphosate label indicates that this statement is a general restriction for all crops and not specifically limited to wheat.

Nature of the Residue:

No metabolism studies are in this submission. We have reviewed glyphosate metabolism in corn, soybeans, wheat, cotton, rice, barley, oats, sorghum, sugarbeets, sugarcane, potatoes, vegetable crops, grapes, coffee and citrus fruits. Glyphosate is not translocated from soil via roots, but translocation does occur from treatment of the aerial plant portions. Metabolism is relatively slow, with less than 5% of the residue in apples present at 4-7 days as the acid. Metabolism studies in rats, rabbits and cows indicate that glyphosate is the primary residue present in animals, with only minor additional amounts of aminomethylphosphonic acid. We have previously concluded the metabolism of glyphosate is adequately understood. The residue of concern is glyphosate per se and its metabolite aminomethylphosphonic acid.

Analytical Method:

The analytical method is entitled "Analytical Residue Method for N-Phosphonomethyl Glycine and Aminomethylphosphonic Acid in Wheat Grain". In brief, the ground sample is blended with 50 ml of chloroform and 150 ml of 0.1 N HCl. The blended material is centrifuged and a 25 gram aliquot passed through the Chelex 100 resin column which is in the Fe(III) form. The Chelex column is eluted with 6 N HCl. The eluant is placed on the anion exchange column of AG-1X8 and eluted with 6 N HCl. The eluant is then taken to dryness on rotary evaporator. The dry sample is taken up in deionized water and analyzed by hplc using a ninhydrin post-column reactor with 400 nm absorbance detector equipped with a 546 nm filter. The method is reported sensitive to 0.05 ppm of glyphosate or aminomethylphosphonic acid in wheat grain and straw.

Crop blanks were <0.05 ppm for both glyphosate and aminomethylphosphonic acid in wheat grain. Wheat straw blanks showed <0.05 ppm to 0.10 ppm glyphosate (levels above 0.05 ppm occurred in the IN and LA samples) and <0.05 ppm aminomethylphosphonic acid.

Average recovery values for glyphosate in grain were 74% (range 53% to 89% at 0.05 to 1.0 ppm fortification levels) and straw 88% (range 65% to 108% at above fortification levels), respectively. Average recovery values for aminomethylphosphonic acid in grain were 82% (range 58% to 106% at 0.05 to 4.0 ppm fortification levels) and straw 84% (range 54% to 108% at same fortification levels), respectively.

A similar method entitled "Analytical Residue Method for N-Phosphonomethyl Glycine and Aminomethylphosphonic Acid in Wheat" is applicable for analysis of glyphosate in wheat milling fractions. The same extraction is followed but either a ninhydrin post-column reactor with 400 nm absorbance detector equipped with a 546 nm filter or o-phthalaldehyde (OPA) post-column reaction and fluorescence detector are used. The second method is reported sensitive to 0.05 ppm of glyphosate or aminomethylphosphonic acid.

We conclude that the method is adequate for the analysis of glyphosate and aminomethylphosphonic acid in wheat.

Residue Data:

We previously concluded the available residue data were not adequate for determination of tolerance levels (R. B. Perfetti, 4/1/83). Specifically we needed more complete geographical representation; analysis of wheat grain, forage, and straw; and a wheat grain milling study to determine if food additive tolerances are required for the processed commodities from wheat. We also concluded that a revised Section B restricting grazing of wheat forage would obviate the need for residue data on wheat forage. The revised Section B does not obviate this need.

In the 1982 data submission, maximum detected levels of glyphosate in wheat grain samples in 6 trials in 4 states (OK-1, ID-1, WA-3, OR-1) were 0.18 ppm at 15 to 84 days after treatment (25% or 33% solution of glyphosate applied as wiper application by pipewick or ropewick applicator). Residues of the metabolite aminomethylphosphonic acid were <0.05 ppm in all grain samples. No residue data were submitted for wheat straw or forage.

Currently, residue studies were conducted in 6 additional locations (CO, ND, NE, IN, CA, and LA). Three of six studies showed no detectable residues of glyphosate in wheat grain or straw. The other three studies showed 0.09-0.97 ppm of glyphosate in grain at 7-35 days PHI. In the IN study (7 days after last application), wheat grain receiving "1 pass" of ropewick application of 33% solution of glyphosate showed 0.24-0.40 ppm of glyphosate and <0.05 ppm aminomethylphosphonic acid, while wheat straw contained 1.4-1.6 ppm glyphosate and <0.05-0.06 ppm of aminomethylphosphonic

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acid. Further in this study, after "2 passes", wheat grain showed 0.78-0.98 ppm glyphosate (aminomethylphosphonic acid <0.05 ppm) and wheat straw showed 2.5-2.9 ppm glyphosate (aminomethylphosphonic acid <0.05-0.07 ppm) at 7 days after treatment. Without decline data, we cannot estimate whether these residue levels would decline below proposed tolerance of 0.25 ppm.

The petitioner suggests that the glyphosate solution may have been of the wrong strength or the tractor pulled the ropewick at a slow rate (thus higher residues). No substantive evidence is presented in support of these contentions.

A majority of the available studies showing no detectable residues have preharvest intervals ("days from last application") far in excess of the 14 day PHI directed on the label. For example, wheat grain samples are available at posttreatment intervals of 7, 12, 15, 21, 28, 33, 35, 38, 48, 59, 66, 74 and 83 days. Thus, only four trials (7 to 21 days posttreatment) provide reasonably reflective supporting residue data for the proposed wiper application with 14 day PHI. There are no true residue decline data. Residues of glyphosate approaching the proposed tolerance level (wheat grain) are shown in some samples at 59 to 74 days after treatment. These data are not useful in support of the 14 day PHI and in our view, indicate that the available data are not adequate to support the proposed tolerance and use.

While most of the trials showed little or no detectable residue of glyphosate in wheat grain at sampling, we question whether the available data are representative of the maximum expected residue levels. We are concerned that ropewick applications appear to be less controllable in regard to amount applied than the usual pesticide application techniques. The condition of the ropewick, drip rate of the ropewick, rate of tractor movement, weed density, and application solution concentration are all confounding factors. The plant stage at time of sampling should be identified by such terms as milk stage, dough, or mature grain. The wheat varieties should be identified. The petitioner should describe the 'hand' application used in the Gretna NE study.

For these reasons, we conclude that the proposed tolerance levels of 0.25 ppm in wheat grain and 0.35 ppm in wheat straw are too low. We are unable to draw final conclusions for glyphosate tolerances for wheat grain and wheat straw based upon available residue data. We believe that additional residue data are needed for wheat grain and wheat straw. The petitioner should provide information on the amount or rate of drip of the herbicidal solution onto the crop. The rate of tractor movement should be described, along with some estimate of weed density. The currently submitted residue data for wiper application of glyphosate on wheat indicate higher glyphosate residues in grain and straw than we would anticipate. The petitioner should discuss any meaningful relationship between conventional dosage rates and selective treatment by wiper application, especially the maximum permitted dosage by wiper. Without definable upper dosage limits, we are concerned that any tolerance which we

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may establish may not be adequate under some circumstances.

Further, either residue data for wheat forage are needed or a practical label restriction against its feed use is needed.

Wheat Milling Study:

Wheat grain containing 0.67 ppm of glyphosate and <0.05 ppm aminomethylphosphonic acid from topical application of 0.3 pounds per acre or 66.6 ppm glyphosate and 1.77 ppm of aminomethylphosphonic acid from application of 3.0 pounds per acre were processed into milling fractions wheat bran, break flour, reduction flour, and wheat shorts.

Glyphosate Residues in Wheat Grain Frationated into Bran, Break Flour, Reduction Flour, and Shorts.								
Location Rate and PHI	Saltillo TN				Mayview MO			
	0.38 #/A		7 Days		3.0 #/A		7 Days	
	<u>Glyp.</u>	<u>CF</u>	<u>AMPA</u>	<u>CF</u>	<u>Glyp.</u>	<u>CF</u>	<u>AMPA</u>	<u>CF</u>
Grain (before Fractionation)*	0.71	--	<0.05	--	78.0	--	2.07	--
Bran	1.66	2.34	0.07	<1.4	121.	1.55	2.58	1.25
Break Flour	0.14	0.20	<0.05	<1.0	22.8	0.29	1.77	0.86
Reduction Flour	0.12	0.17	<0.05	<1.0	22.8	0.29	1.68	0.81
Shorts	1.20	1.69	<0.05	<1.0	94.7	1.21	2.51	1.21

* PPM after drying to milling condition.
CF = Concentration Factor

Glyphosate residues concentrated about 2.3X in bran and shorts, and levels in break and reduction flours are less than the initial glyphosate levels. Thus, the proposed food additive tolerances of 0.4 ppm in wheat bran and 0.3 ppm in wheat shorts are not appropriate. Based on the submitted data, the proposed levels are not high enough to cover expected residue levels. Food additive tolerances for bran and shorts should be expressed in terms of "Wheat milling fractions (Excluding flour)". A revised Section F proposing such food additive tolerances is needed. A level of 3X the level found in the raw agricultural commodity would be appropriate, at the time we can draw final conclusions on the expected levels in grain.

TOX has concluded (W. Dykstra, 3/19/85) that food additive tolerances for glyphosate in or on wheat milling fractions are not appropriate due to the Delaney rule.

Meat, Milk, Poultry and Eggs:

Wheat grain, forage, straw and milling fractions are all major animal feed items. We previously concluded that the dairy cattle feeding study IBT No. 651-3775 was invalid, and no tolerances for glyphosate in a cattle feed item could receive a favorable recommendation until the existing study is found to be valid or until a new study is submitted and reviewed (R. B. Perfetti, 4/1/83). However, RCB has recently examined validation data for IBT No. 8

651-3775. Based upon a cattle palatability study reportedly showing no significant difference in feed consumption or milk production, RCB now considers the Milk and Meat Residue Study with Glyphosate and Aminomethylphosphonic Acid valid (E. Zager, 1/4/85).

Feeding studies have been carried out in cattle, poultry, and swine using a 3:1 ratio of glyphosate and aminomethylphosphonic acid. At the 100 ppm feeding level no detectable (<0.025 ppm) residue of glyphosate and its metabolite aminomethylphosphonic acid were found in milk or eggs and none (<0.05 ppm) were found in muscle tissue or fat of cattle, swine or poultry. Residues were detected in kidney and liver.

Residues were detectable in kidney of cattle and swine at 30 and 100 ppm feeding levels (10 ppm level in cattle was not analyzed). At 30 and 100 ppm dietary levels, residues of glyphosate per se in cattle were 0.67 and 1.18 ppm, and aminomethylphosphonic acid residues were 0.13 and 0.46 ppm respectively. Residues of glyphosate in swine kidney were 0.11, 0.42, and 0.93 ppm at the 10, 30, and 100 ppm feeding levels. Aminomethylphosphonic acid in swine kidney (0.2 ppm) were detectable at the 100 ppm feeding level only.

Based upon these data, we conclude that the established tolerance of 0.5 ppm in the kidney and liver of cattle, goats, hogs, horses, poultry and sheep will not be exceeded by the additional dietary burden posed by wheat grain, straw, forage, hay, and milling fractions used for animal feeds.

No detectable residues of glyphosate or its metabolite were found in meat, fat, meat byproducts (except kidney and liver), milk, or eggs, and therefore, no secondary residues are likely to occur in these commodities as a result of changes in established tolerance levels contemplated in wheat grain, wheat straw, and in wheat milling fractions (excluding flour).

OTHER CONSIDERATIONS:

International Tolerances:

Since there are no Codex, Canadian, or Mexican tolerances for glyphosate on wheat grain, wheat straw, wheat bran or wheat shorts, we anticipate no problems of compatibility.

cc: R.F., Circu, Reviewer, TOX, EEB, EAB, FDA, PP 3F2809, W. Boodee,
RDI:Section Head:RSQuick:Date:4/17/85:RDSchmitt:Date:4/18/85
TS-769:RCB:Reviewer:R6Cook:RWCook:557-7377:CM#2:RM:810:4/16/85

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INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL: Glyphosate

PETITION NO. PP 3F2809/FAP5H5450

R. W. Cook

3/28/85

CCPR NO. _____

Codex Status

Proposed U.S. Tolerances

☐ No Codex Proposal Step
6 or above

Residue (if Step 9):

Residue:
Glyphosate and its metabolite
aminomethylphosphonic acid.

Crop(s) Limit (mg/kg)

Crop(s) Tol. (ppm)

Wheat grain	0.25
Wheat straw	0.35
Wheat bran *	0.4
Wheat shorts *	0.3

CANADIAN LIMIT

MEXICAN TOLERANCIA

Residue:

Residue:

Crop Limit (ppm)

Crop Tolerancia (ppm)

Comments: Proposed Food Additive Tolerances.

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