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

OCT 24 1986

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#6F3380/6H5502. Glyphosate (Roundup®) in or on Soybeans. ~~Evaluation~~ of Analytical Method and Residue Data. (Acc. #261638; RCB #889 and #890)

FROM: W. T. Chin, Chemist
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

W. T. Chin

THRU: Philip V. Errico, Section Head
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

P. Errico

TO: Robert Taylor, PM #25
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Monsanto Agricultural Products Company proposes to increase the tolerances as established under 40 CFR §180.364 for the combined residues of the herbicide glyphosate, N-(phosphonomethyl)glycine and its metabolite, aminomethylphosphonic acid (AMPA) for soybeans at 20 ppm (now 6 ppm), soybean hay at 200 ppm (now 15 ppm) and for soybean hulls at 100 ppm (now 20 ppm) under 40 CFR §561.253 based on pre-harvest applications.

Tolerances for the combined residues of glyphosate and AMPA have been established (40 CFR §180.364 and §561.253) on a variety of crops and processed products ranging from 0.1 to 200 ppm. A number of pesticide petitions are pending including PP# 3F2809, wheat grain; PP#3E2893, fruiting vegetables and PP#3E2930, small fruits.

Dr. T. F. Armstrong of Monsanto explained by phone to W. T. Chin of RCB on 9/18/86 that the so-called "soybean hay" is left on the ground after harvest of the soybeans. This dried plant residue remaining after harvest of the beans is more appropriately referred to as "soybean straw". Dr. Armstrong also indicated that soybean forage should remain unchanged at its established tolerance of 15 ppm.

CONCLUSIONS

1a. For the proposed use, the formulation of glyphosate is Roundup® (EPA Reg. No. 524-308-AA) and contains 4 lbs of the isopropylamine salt per gallon corresponding to 3 lbs of glyphosate acid active ingredient per gallon. All of the inerts in the formulation are cleared for use under 40 CFR 180.1001.

1b. The petitioner has to fill the following data gaps specified in the Product Chemistry Chapter of Glyphosate Registration Standard issued by RCB on 7/15/85: §61-2. Description of beginning materials and manufacturing process. §61-3. Discussion of formation of impurities. §62-1. Preliminary analysis of products. §62-2. Certification of ingredient limits. §62-2. Certification of ingredient limits. §62-3. Analytical methods to verify certified limits. §63-4. Oder. §63-7. Density. §63-8. Solubility. §63-9. Vapor pressure. §63-11. Octanol/water partition coefficient. §63-12. pH. §63-13. Stability.

2a. The petitioner is requested to submit detailed information regarding specific rates and application instructions for the current petition. The complete Roundup® label should be provided.

2b. In the submitted "Directions for Use," the sentence "Do not feed or graze treated areas within 25 days after preharvest application" should be modified to read "Do not graze or harvest treated crop for livestock feed within 25 days of last preharvest application."

2c. The so-called "soybean hay" which the petitioner is proposing a tolerance at 200 ppm is understood to be "soybean straw", the dried plant residue remaining on the ground after harvest of the soybeans. The petitioner is requested to clarify this point by submitting a revised Section F.

3a. The nature of the residue in soybeans is adequately delineated. The residue of concern consists of the parent compound and its metabolite, AMPA.

3b. As indicated in Glyphosate Registration Standard (7/15/85), "metabolism studies using ruminants and poultry are required. Animals must be dosed for at least three days with ^{14}C-glyphosate at a concentration in the total diet which will result in sufficient residues in the tissues, milk, and eggs for characterization. Animals must be sacrificed within 24 hours of the final dose (milk and

eggs must be collected twice daily). The distribution, characterization, and quantification of residues must be determined in eggs, milk, muscle, fat, kidney, and liver."

4a. RCB concludes that the new residue method submitted with this petition is better and faster than the old enforcement method published in PAM II and that a method trial for this new method will be needed. The tolerance recommendation will not be held up for the method trial. For method trial purposes, the petitioner is requested to re-submit this method without the "Confidential" label.

4b. If animal metabolism studies (Conclusion 3b) indicate new metabolites in need of regulation, additional methodology and feeding studies may be needed.

5. Since the field trials were conducted in 1979 and the dates of analysis of the samples are not given, RCB cannot determine the storage periods of the samples analyzed. Therefore, RCB is unable to determine the adequacy of the residue data submitted for the requested tolerance changes without the support of adequate storage stability data. The petitioner should submit information on the conditions and period of sample storage.

6a. Previous feeding studies on cattle, poultry and swines using a 3:1 ratio of glyphosate and AMPA at dietary levels of 10, 30 and 100 ppm indicated that no detectable (<0.025 ppm) residues of glyphosate and AMPA were found in milk or eggs and none (<0.05 ppm) were found in muscle or fat of cattle, swine or poultry from the 100 ppm feeding level (PP#5F1536). However, if the metabolism studies requested in Conclusion 3b above identify additional residues of toxicological concern, new feeding studies may be needed.

7. The International Residue Limit Status sheet is attached. There are no Codex or Mexican limits for glyphosate on soybeans, soybean hay and soybean hulls. There is a Canadian "negligible residue type limit" of 0.1 ppm on all food crops, From the magnitude of the residue levels on soybean for the proposed use, RCB cannot harmonize the U.S. and Canadian tolerances.

RECOMMENDATION

RCB recommends against the proposed increase in the established tolerances for the combined residues of glyphosate and AMPA in soybeans, soybeans hay and hulls because of the reasons specified in the above Conclusions Nos. 1b, 2a, 2b, 2c, 3b, 5 and 6a.

PM NOTE: Please provide the complete label for Roundup® (Conclusion 2a).

DETAILED CONSIDERATIONS

Manufacturing and Formulation

The manufacturing process for technical glyphosate was submitted in conjunction with PP#6E1809 and discussed in detail in D. Duffy's 11/30/76 review (PP#6G1826). For the present use, glyphosate is formulated as Roundup® (EPA Reg. No. 524-308-AA) and contains 4 lbs of the isopropylamine salt per gallon corresponding to 3 lbs of glyphosate acid active ingredient per gallon. All of the inerts in the formulation are cleared for use under 40 CFR 180.1001 (see review of R. Perfetti, 4/1/83, PP#3F2809)

The petitioner has to fill the following data gaps specified in the Product Chemistry of Glyphosate Registration Standand issued by RCB on 7/15/85:

§61-2. Description of beginning materials and manufacturing process.
§61-3. Discussion of formation of impurities.
§62-1. Preliminary analysis of products.
§62-2. Certification of ingredient limits.
§62-2. Certification of ingredient limits.
§62-3. Analytical methods to verify certified limits.
§63-4. Oder.
§63-7. Density.
§63-8. Solubility.
§63-9. Vapor pressure.
§63-11. Octanol/ water partition coefficient.
§63-12. pH.
§63-13. Stability.

Proposed Use

The submitted "Directions for Use" indicate that this product may be applied by both ground or aerial application equipment prior to the harvest of soybeans after pods have lost all green color. It is not recommended that soybeans grown for seed be treated because a reduction in germination or vigor will occur. The following statements are included on the label: Allow a minimum of 7 days between application and harvest of soybeans. Do not feed or graze treated areas within 25 days after preharvest application. Do not apply more than one quart per acre of this product by air. Do not apply by air in California.

The above sentence "Do not feed or graze treated areas within 25 days after preharvest application" should be modified to read "Do not graze or harvest treated crop for livestock feed within 25 days of last preharvest application."

Only a small portion of the Roundup® label has been provided. The complete label, with application rates, should be submitted.

Nature of the Residue

No new metabolism studies are submitted in this petition. However, metabolism studies have been conducted previously on a variety of crops: soybeans, corn, wheat, and cotton (PP#5F1536, Acc. #118954). These studies demonstrate that glyphosate is not readily absorbed from the soil via the root system of plants. However, translocation does occur when the compound is applied to aerial plant parts. Degradation occurs by C-N bond cleavage to form AMPA and glyoxylate which are further catabolized with subsequent incorporation into natural plant constituents. RCB has concluded that the nature of the residue in soybeans has been adequately delineated. The residue of concern consists of the parent compound and its metabolite, AMPA (see R. Perfetti's 4/1/83 memo, PP#3F2809).

Metabolism studies in rats, rabbits and cows indicated that parent compound makes up the major portion of the residue in mammals with only trace amounts of AMPA being observed (R. Perfetti's 4/1/83 memo, PP#3F2809). However, according to Glyphosate Registration Standard issued by RCB on 7/15/85, "metabolism studies using ruminants and poultry are required. Animals must be dosed for three days with ^{14}C-glyphosate at a concentration in the total diet which will result in sufficient residues in the tissues, milk, and eggs for characterization. Animals must be sacrificed within 24 hours of the final dose (milk and eggs must be collected twice daily). The distribution, characterization, and quantification of residues must be determined in eggs, milk, muscle, fat, kidney, and liver."

Analytical Methods

The petitioner submitted a new method entitled "Analytical Residue Method for N-Phosphonomethylglycine and Aminomethylphosphonic Acid In Soybean Fractions." The two compounds are first removed from soybean sample extracts by elution through Chelex® 100 resin in the Fe(III) form and then eluted from the resin with hydrochloric acid and the iron is removed using an anion exchange resin. After concentration to dryness to remove the hydrochloric acid, samples are analyzed using a two column switching HPLC equipped with a ninhydrin post-column reactor and an absorbance detector. The sensitivity limit of this method for glyphosate and AMPA is 0.05 ppm. Adequate chromatograms and calculations are submitted. For soybean oil and soapstock, limits of detection are 0.1 and 0.2 ppm, respectively.

The present enforcement method published in PAM II consists of extraction with water followed by isolation of parent and metabolite by ion exchange chromatography. The compounds are then converted to their corresponding N-trifluoromethyl derivatives through derivatization steps and determined via GLC using a phosphorus specific flame photometric detector. The method has a successful method trial on soybeans and beef liver (PP#5F1536). However, this published method is time consuming and RCB has had reports from FDA and state agencies of difficulty in running the PAM II method (PP#0F2329). However, if metabolism studies indicate new metabolites, different method may be needed.

The reported recoveries for this HPLC procedure are summarized in Table 1.

Table 1. Recovery Data for Glyphosate and AMPA in Various Soybean Fractions

Matrix (Soybean)	Fortification (ppm)	Recoveries (%)	
		Glyphosate	AMPA
Whole Grain	0.05 - 20	97.3	92.4
Hay	0.05 - 300	99.1	93.9
Hulls	0.5 - 100	99.4	101.0
Oil	0.05 - 0.75	95.7	81.6
FF Meal	0.5	84.2	82.9
Soapstock	0.5	88.6	70.3

RCB concludes that this new residue method is better and faster than the old enforcement method published in PAM II and that a method trial for this new method will be needed. However, the tolerance recommendation will not be held up for the method trial. The method should not be labeled "Confidential." If additional metabolites in need of regulation are uncovered in the requested animal metabolism studies, additional methodology will be needed.

Residue Data

The residue data currently submitted were generated from the field trials conducted in 1979 in Ark., Miss., Ky. and Iowa states which represent the major soybean growing areas in this country. Prior to the preharvest applications, two to three recirculating sprayer (RCS) treatments with Roundup® herbicide had been applied early in their growth stage. The combined residue data of glyphosate and AMPA in the soybeans and hay are summarized in Table 2, and the combined residues of glyphosate and AMPA in soybean fractions are summarized in Table 3.

The data submitted indicated that samples of both soybean grains and "soybean hay" were taken on the same harvest date, 11/11/97. This confirms Dr. T. F. Armstrong's 9/18/86 explanation that the so-called "soybean hay" is the dried plant residue remaining on the ground after harvest of the soybeans. This dried plant residue after harvest of the beans is more appropriately referred to as "soybean straw". The petitioner is requested to clarify this point by submitting a revised Section F.

No storage stability data are provided in the current submission. However, some storage stability data for glyphosate on soybeans were submitted in conjunction with PP#7F1971/7H5168 and indicated that no appreciable losses of residues on soybeans, soybeans forage and hay were found after being held under frozen conditions over a period of 21 months.

Table 2. Maximum Combined Residue Data of Glyphosate and AMPA in Soybeans and Hay Following RCS and Preharvest Topical Treatment with Roundup® Herbicide

Location	DART*	DAPT**	Total Rate (lb a.i./A)	Preharvest (lb a.i./A)	Combined Residues (ppm) Grain	Hay
Bruins, Ark.	64,73	7,10	5.25	0.75	1.01	7.25
	"	"	6.00	1.50	1.50	14.32
	"	"	7.50	3.00	1.68	34.06
	"	"	9.00	4.50	0.93	31.30
Bruins, Ark.	73	16	5.25	0.75	1.22	2.02
	"	"	6.00	1.50	1.64	5.27
	"	"	7.50	3.00	1.19	12.39
	"	"	9.00	4.50	0.60	21.16
Banks, Miss.	37,37	15,9	4.50	0.75	15.98	7.29
	"	"	5.25	1.50	13.59	15.04
	"	"	6.75	3.00	13.74	21.35
	"	"	8.25	4.50	19.32	28.53
Princeton, Ky.	48,62	11,13	14.25	0.75	3.75	4.31
	"	"	15.00	1.50	4.45	6.99
	"	"	16.50	3.00	9.78	18.41
	"	"	18.00	4.50	7.71	31.11
Princeton, Ky.	62	25	14.25	0.75	1.82	3.60
	"	"	15.00	1.50	2.41	5.07
	"	"	16.50	3.00	0.62	8.94
	"	"	18.00	4.50	7.82	17.25
Adel, Iowa	75,75	11,8	14.25	0.75	0.06	12.42
	"	"	15.00	1.50	0.10	50.01
	"	"	16.50	3.00	0.20	89.48
	"	"	18.00	4.50	0.71	203.81

*DART: Days after last RCS treatment until sample taken for plots receiving preharvest topical treatments.

**DAPT: Days after preharvest topical treatment until sample taken for plots receiving preharvest topical treatments.

Table 3. The Combined Residues of Glyphosate and AMPA in Soybean Fractions

Processed Fractions	Residues Determnined (ppm) 0.0 lb/A	0.75 lb/A	3.0 lb/A
Whole soybean grain	0.10	10.99	13.74
Fat-free meal	0.07	10.53	13.77
Hulls	0.12	45.61	65.56
Crude oil	<0.10	<0.10	0.11
Soapstock	<0.20	<0.20	<0.20

Since the field trials were conducted in 1979 and the dates of analysis of the samples are not given, RCB cannot determine the storage periods of the samples analyzed. Therefore, RCB is unable to determine the adequacy of the residue data submitted for the requested tolerance changes without the support of adequate storage stability data. In addition, even if the storage stability data are supportive, RCB still cannot evaluate the adequacy of the residue data submitted without detailed information regarding specific rates and application instructions. The petitioner should submit a revised Section B giving the complete proposed use, including specific rates and application instructions (see Conclusion 2a).

Meat, Milk, Poultry and Eggs

Previously, data of feeding studies have been submitted in conjunction with PP# 5F1536 including studies on cattle, poultry and swines using a 3:1 ratio of glyphosate and AMPA at dietary levels of 10, 30 and 100 ppm. No detectable (<0.025 ppm) residues of glyphosate and AMPA were found in milk or eggs and none (<0.05 ppm) were found in muscle or fat of cattle, swine or poultry from the 100 ppm feeding level. However, detectable residues were found in kidney and liver of the 30 and 100 ppm feeding levels (the cattle tissues from the 10 ppm feeding level were not analyzed) with the highest levels in kidney. In the kidney of cattle, the combined residues of of glyphosate and AMPA at the 30 ppm dietary level was 0.70 ppm, and at the 100 ppm dietary level was 1.64 ppm. The established tolerance for the combined residues of glyphosate and AMPA in the kidney and liver of cattle is 0.5 ppm (§180.364). The maximum livestock exposure from the existing and proposed tolerances are shown in Table 4 on the next page.

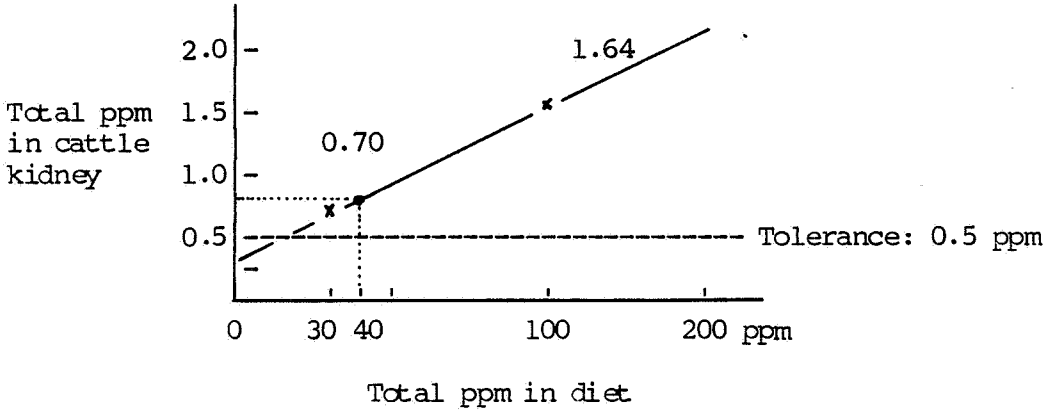
Table 4. Estimation of Maximum Livestock Exposure to The Existing and Proposed Tolerances

Crop	Tolerance (ppm)	% of livestock Diet			Exposure to Livestock Diet		
		Beef	Dairy	L. Hens	Beef	Dairy	L.Hens (ppm)
Soybeans	20*	25	30	50	5.0	6.0	10.0
"Soybean hay"**	200*	10	10	-	20.0	20.0	-
Soybean hulls	100*	10***	10	-	10.0	10.0	-
Peanut hay	0.5	15	25	-	0.1	0.1	-
Cotton forage	15	20	-	-	3.0	-	-
Alfalfa	20****	10	10	-	2.0	2.0	-
Sum		90	85	50	40.1	38.1	10.0

* Currently proposed tolerances; all others are established tolerances
** The term "soybean hay" here is actually "soybean straw".
*** The maximum is 20%. Since 25% soybeans is used, soybean hulls is reduced to 10% for this worst case calculation.
**** 10% spot application; 200 ppm x 10% = 20 ppm (PP#1F~~2581~~2518).

Data shown in Table 4 indicate that at the proposed tolerances of soybeans, "soybean hay" and soybean hulls and the existing tolerances of the other three feed commodities selected, the maximum exposure of dairy cow to these feeding commodities is around 40 ppm which is above the 30 ppm level of the previous feeding studies. At the maximum exposure of 40 ppm level, the total residues of glyphosate and AMPA in cattle kidney, as indicated on the chart below, is estimated as high as 0.8 ppm which is higher than the established 0.5 ppm tolerance in cattle kidney. Therefore, these data indicate that the existing tolerance in cattle kidney may not support the proposed tolerances in or on soybeans, "soybean hay" (actually soybean straw) and hulls. RCB withholds a tolerance recommendation on livestock kidney until the documents specified in Conclusion 2a and 5 are submitted.

In addition, if the metabolism studies requested in Conclusion 3b identify additional residues of toxicological concern, new feeding studies at a higher level will be needed.



OTHER CONSIDERATIONS

The International Residue Limit Status sheet is attached. There are no Codex or Mexican limits for glyphosate on soybeans, soybean hay and soybean hulls. There is a Canadian "negligible residue type limit" of 0.1 ppm on all food crops, From the magnitude of the residue levels on soybeans for the proposed use, RCB cannot harmonize the U. S. and Canadian tolerances.

cc: R.F , EAB PP#6F3380/6H5502, EEB, PM#25, TOX, W.T.Chin, PMSD-ISB
RDI: P.V.Errico(10/23/86), R.D.Schmitt(10/23/86)
TS-769: RCB: CM#2, RM812,557-4352, W.T.Chin,wc(10/24/86)

F. Lees
6/17/86

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Glyphosate

CCPR NO.

PETITION NO. 6F3380/6H5502

Reviewer: W. T. Chin

Codex Status

[/] No Codex Proposal Step 6 or above

Residue (if Step 9):

Crop(s) Limit (mg/kg)

Proposed U.S. Tolerances

Residue: Glyphosate + aminomethyl-phosphonic acid

Crop(s)	Tol. (ppm)
Soybeans	20
Soybeans Hay	200
Soybeans Hull	100

CANADIAN LIMIT

Residue: glyphosate

Crop	Limit (ppm)
All food crops	0.1 *

MEXICAN TOLERANCIA

Residue:

Crop	Tolerancia (ppm
None	

NOTES:

* Negligible residue type limit