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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MAR 21 1996

MEMORANDUM

SUBJECT: PP#8F03673, Evaluation of Analytical Method and Residue Data. Glyphosate on Corn. Glyphosate Isopropylamine Salt Label Amendment. Chemical# 417300 and 103601, DP Barcodes: D216229 and D216230, CBTS#s: 15700 and 15701, MRID#: 436557.

FROM: William D. Cutchin, Chemist
Tolerance Petition Team I
Chemistry Branch I: Tolerance Support
Health Effects Division (7509C)

THROUGH: Ed Zager, Acting Chief
Chemistry Branch I: Tolerance Support
Health Effects Division (7509C)

TO: Robert Taylor, PM Team 25
Fungicide Herbicide Branch
Registration Division (7505W)

and

Debbie McCall, Acting Section Head
Risk Assessment and Analysis Branch
Health Effects Division (7509C)

Monsanto Agricultural Co. requests increases in the tolerances of the herbicide glyphosate (N-phosphonomethyl glycine) on corn grain to 1 ppm, corn fodder (stover) to 100 ppm, and the kidney and liver of cattle, goats, hogs, horses, poultry, and sheep to 1 ppm, and the establishment of a permanent tolerance on aspirated grain fractions at 200 ppm. The registrant also requests the amendment of the Roundup® Herbicide (EPA Reg. No. 524-445) label for a new preharvest use (i.e., prior to the harvest of the mature corn grain). An increase in the corn forage tolerance is not requested since corn forage would be harvested before the preharvest application takes place.

Tolerances for the combined residues of glyphosate and its metabolite aminomethylphosphonic acid (AMPA) exist on corn grain and fodder as part of the dated grain and forage grasses crop

1/12

groups at 0.1 ppm and 0.2 ppm respectively (40 CFR § 180.364). Food additive and feed additive tolerances are established under 40 CFR §185.3500 and §186.3500, respectively, for the combined residues of glyphosate and AMPA.

The submission is intended to replace data generated by Craven Labs. Because the use pattern requested by the registrant is significantly higher than the original submission, no comparison between the present data and the Craven data is requested.

The Product and Residue Chemistry Chapters for the Glyphosate Reregistration Eligibility Decision Document (DP Barcode: D183202, CBRS#: 10665) were completed, 10/27/92. The HED Metabolism Committee has determined that AMPA does not need to be regulated and should be dropped from the tolerance expression in the future (Memo, R. Perfetti, 8/19/92).

Conclusions

1. Product chemistry data requirements for glyphosate are adequately fulfilled (Product Chemistry Chapter, 10/27/92).

2. Use directions described in Section B of PP#8F3673 adequately describe the proposed registration of glyphosate for the treatment of corn. The submitted label does not indicate that the use of adjuvants is allowed with this use. The residue data presented here were generated without the use of adjuvants. If the registrant desires the use of adjuvants, additional residue data will be required.

3. The metabolism of glyphosate in plants is adequately understood. The residue of concern in plants is glyphosate *per se*.

4. The metabolism of glyphosate in animals is adequately understood. The residue of concern is glyphosate *per se*.

5. Analytical methods are available for enforcement of the proposed glyphosate tolerances in/on corn commodities.

6. Corn grain, forage, fodder, and aspirated grain fractions are raw agricultural commodities. Corn starch, refined oil, grits, meal, and flour are processed commodities. Corn grain, forage, fodder, aspirated grain fractions, and milled byproducts are feedstock items.

7a. Residue data submitted in support of PP#8F3673 are inadequate. Considering the variability observed in residues in the submitted field trials, these studies reflect an insufficient number of geographically represented sites.

7b. Section F indicated the tolerances are to be established on corn. The correct terminology is corn, field, grain and corn,

field, fodder.

8. Processing data submitted in support of PP#8F3673 are inadequate. While glyphosate residues appear to concentrate on corn aspirated grain fractions, the rate varies considerably within the presented processing studies. The registrant must provide a rationalization for the disparity between the two concentration factors. The higher concentration factor will be used to calculate the tolerance on aspirated grain fractions and from that the dietary burden until a suitable explanation is received. With the HAFT of 0.54 ppm and 395x concentration, the 200 ppm tolerance is appropriate for the time being.

9. Corn grain, forage, fodder, aspirated grain fractions, and milled byproducts are animal feed items. The dietary burden to livestock from this proposed use, and the transfer of glyphosate residues from livestock feed items to meat, milk, poultry, and eggs are covered by established tolerances with the exception of kidney and liver, for which the 4 ppm tolerances recommended by CBTS in PP#4F4312 need to be established. The list of animal commodities should be deleted from Section F.

10. Codex MRL's for the residues of glyphosate exist on maize and the straw and fodder, dry of cereal grains at 0.1 and 100 ppm respectively. Mexican limits on maize exist at 0.1 ppm. Canadian limits on 'all other food crops' exist at 0.1 ppm. The registrant should propose and support an increase in the Codex limit for maize to 1 ppm.

Recommendations

For the reasons cited in conclusions 7a, 7b, 8, and 9 above, CBTS recommends against the permanent increase of glyphosate tolerances in or on field corn grain to 1 ppm, field corn fodder to 100 ppm, the kidney and liver of cattle, goats, hogs, horses, poultry, and sheep to 1 ppm and the establishment of a glyphosate tolerance in/on aspirated grain fractions at 200 ppm.

However, based on the submitted field trials, provided (1) an adequate explanation for the disparity in concentration factors from the processing studies is presented, (2) provided Section F is corrected, and (3) the liver/kidney tolerances of 4 ppm in PP#4F4312 are established, CBTS could recommend for time limited tolerances while additional residue data are generated. The corrected Section F must list the above items at the above levels with the deletion of the animal commodities.

A DRES run using the above proposed tolerance of 1 ppm for field corn grain may be initiated at this time.

Detailed Considerations

Manufacture and Formulation

Some data requirements are still outstanding for the trisodium salt technical, both the 94% and 75% isopropylamine acid technical. The RED Document also concluded that the registrant must either certify that the suppliers of beginning materials and manufacturing processes for the glyphosate technical products and manufacturing-use products have not changed since the last comprehensive Product Chemistry Chapter or submit a complete updated product chemistry data package (Product Chemistry Chapter, 10/27/92). This is not a deficiency for this submission. No further data are necessary for this proposed use.

Proposed Use

The proposed use directions, Section B, are adequate. The product Roundup® Herbicide (EPA Reg. No. 524-445) is applied by ground equipment at a rate of 3 qt (2.25 lb ai)/A or by air at 1 qt (0.75 lb ai)/A. The applications are made at 35% or less grain moisture and the corn is physiologically mature (black layer formed). A seven day PHI is indicated. Corn for use as forage would have already been harvested before this product would be applied. The submitted label does not indicate that the use of adjuvants is allowed with this use. The residue data were generated without the use of adjuvants. If the registrant desires the use of adjuvants, additional residue data will be required. No further label information is necessary for this proposed use.

Nature of Residue - Plants

No plant metabolism studies were submitted with this petition. Nature of residue studies have been performed on corn, cotton, soybeans, and wheat. The studies indicate that foliarly applied glyphosate is readily absorbed and translocated. The residue of concern is glyphosate *per se* (Residue Chemistry Chapter, 10/27/92). No further data are necessary for this proposed use.

Nature of Residue - Animals

No animal metabolism studies were submitted with this petition. Nature of residue studies have been conducted using lactating goats and laying hens fed a mixture of glyphosate and AMPA. Metabolism studies have also been conducted in rats, rabbits, and cows. The residue of concern is glyphosate *per se* (Residue Chemistry Chapter, 10/27/92). No further animal metabolism data are necessary for this proposed use.

Analytical Methods - Enforcement

Adequate enforcement methods are available for analysis of residues of glyphosate in or on plant and animal commodities. These methods include a GLC method (PAM II, Method I) and an HPLC method with fluorometric detection. The HPLC method has undergone successful Agency validation and was recommended for inclusion in PAM II (Residue Chemistry Chapter, 10/27/92).

The method used in the submitted studies was similar to the validated HPLC method. The method consisted of the extraction of glyphosate residues from the plant residues with dilute hydrochloric acid (HCl). The extract solution was eluted through a resin in the Fe(III) form, which retains glyphosate by chelation. The iron salts were eluted from the resin with 6 N HCl. The isolated glyphosate iron salt was then applied to a strong anion exchange resin and eluted with 6 N HCl to remove the iron and obtain the glyphosate free acids. After concentration to dryness, the samples were redissolved in water and analyzed by HPLC with fluorometric detection. The analytical instrument used column switching and an o-phthalaldehyde post-column reactor to form a fluorescent derivative. Recoveries from corn grain control samples fortified with glyphosate from 0.05 to 2 ppm ranged from 64 to 91% averaging 77%. Recoveries from corn fodder control samples fortified with glyphosate from 0.05 to 200 ppm ranged from 62 to 114% averaging 84%. The performing laboratory, Monsanto Agricultural, included sample chromatograms and calibration curves. No further information is necessary for this proposed use.

Analytical Methods - Multiresidue

The Pestrak data base (1990) indicates that recoveries are not likely for glyphosate under FDA Multiresidue Methods. No further data are required for this proposed use.

Magnitude of Residue

Considering the variability observed in residues in the field trials (see Table I below), the residue data submitted with this petition are insufficient to establish the requested tolerances. The results of twelve corn residue studies were submitted here. Eleven studies were conducted in Region V - Michigan, Iowa, Missouri, Illinois, Wisconsin, Indiana, Ohio, Kentucky, Minnesota, Nebraska, and South Dakota and one study in Region VI- Texas. As specified in the Agency's June 1994 guidance on number and location of field trials, a total of twenty successful residue studies with the correct geographic diversity are necessary to establish tolerances in/on field corn. Eight more studies with the correct geographic diversity are necessary to establish the requested tolerances. CBTS has no objection to these additional trials being conducted in conjunction with a conditional registration and time limited tolerance. Glyphosate residues appear to concentrate on

some corn processed commodities (see "Processing Studies" below).

Section F must be corrected. The terminology of the RAC and processed commodities for which increases in tolerances are requested are incorrect and must be resubmitted.

Commodity	ppm
corn grain, field	1
corn fodder, field	100
aspirated grain fractions	200

Field Studies

For each of the residue studies, there was a control plot and treated plot. Roundup® Herbicide was applied to the treated plot to mature corn plants by ground equipment at the maximum rate of 3 qt (2.25 lb ai)/A. Grain and fodder were harvested six to eight days after application. The results of the analysis indicate that residues of glyphosate on corn grain ranged from ND to 0.54 ppm averaging 0.08 ppm. The corn fodder samples had 3.7 to 92 ppm glyphosate residues averaging 35 ppm. Sample chromatograms, standards, and calibration curves are included in the submission.

Table I: Glyphosate Residues Found in Field Residue Studies

State	Corn Grain avg ppm (a) Found	Corn Fodder avg ppm (a) Found
Michigan	0.02	3.66
Iowa*	0.02	27.6
Missouri	0.05	8.80
Illinois*	0.07	22.8
Wisconsin	0.01	17.7
Indiana	0.01	8.45
Ohio	0.54 (b)	10.6
Kentucky	0.05	43.4
Minnesota	0.19	81.7
Nebraska	0.03	91.7 (c)
South Dakota	ND	61.9
Texas	0.04	17.7

* Corn grain samples used in processing study.
(a) Average of duplicate samples.
(b) Highest corn grain residue found 0.569 ppm.

(c) Highest corn fodder residue found 94.255 ppm.

Processing Studies
Samples of field corn from the Iowa and Illinois studies were milled to produce corn processed commodities. The corn grain was milled in a manner to simulate common practice. A batch process was used instead of a continuous mode due to the small sample size.

The whole corn grain samples were cleaned and dried by aspiration and screening. Grain dust was analyzed in two fractions: less than and greater than 2540 μm. The sample > 2540 μm consisted of large pieces of cob, stalk or leaf up to 10 cm long which is considerably outside the normal range of grain dust. The whole grain samples were then divided for dry and wet milling.

For dry milling, the sample was conditioned to 20-22% moisture and tempered. The sample was then impact milled. The milled sample, cornstock, was dried at 130-160 °F for 30 minutes. After cooling, the cornstock was passed over a 1/8 in. shaker screen. The material left on the screen was further processed into large grits, germ, and bran. The germ was further processed into crude and refined oil. The material passing through the screen was processed further into small and medium grits, coarse meal, meal, and flour. The dry milled samples analyzed for glyphosate residues were the grain dust, cleaned whole grain, composite grits, composite meal, flour, and crude and refined oils.

For wet milling the cleaned whole grain was steeped in 120-130 °F, 0.1-0.2% sulfurous acid for 22-48 hrs. After steeping, the whole corn sample was milled and the ground product, cornstock, floated in salt water to remove the germ. The remaining cornstock was further ground to remove the germ, bran, gluten, and starch. The germ was further processed into crude and refined oil. The wet milled samples analyzed for glyphosate residues were the whole starch and crude and refined oils.

The results of the analysis of the individual processed commodities are listed in Table II. The concentration factors are calculated by dividing the glyphosate level found in the processed commodity by the glyphosate level found on the corresponding RAC. The highest concentration factor was 672 on grain screenings from Illinois. The requested tolerance for aspirated grain fractions is based on the highest average field trial (HAFT) grain residue found, 0.54 ppm, multiplied by the highest concentration factor found on grain dust, 395. A tolerance on milled byproducts would be calculated from the highest average grain residue, 0.54 ppm, multiplied by the average concentration factor found on dry milled commodities, 1.12 ((1.71 + 0.52)/2), found on flour. The result of this calculation, 0.6 ppm (0.54 ppm * 1.12), is lower than the requested tolerance on the corn grain, therefore no feed additive tolerance is required for milled byproducts.

Current CBTS policy indicates that the average concentration factors found in processing studies are to be used to calculate tolerances on processed commodities. While the difference in the concentration factors used to calculate the tolerance for dry milled commodities is not significant, 1.71 vs 0.52, the difference between the concentration factors for grain dust is significant, 395 vs 14.4 (27x). Averaging the grain dust concentration factors from two studies would cut the tolerance on aspirated grain fractions in half. The registrant must provide a rationalization for the disparity between the two concentration factors. The higher concentration factor will be used to calculate the tolerance on aspirated grain fractions and from that the dietary burden until a suitable explanation is received. With the HAFT of 0.54 ppm and 395x concentration, the 200 ppm tolerance is appropriate for the time being.

Table II: Results of the Corn Processing Study

Commodity	Illinois		Iowa	
	Found ppm	Conc. Factor	Found ppm	Conc. Factor
Clean Grain	0.02	NA	0.05	NA
Grain Dust(1)	8.30	395	0.64	14.4
Grain Screenings	14.1	672	0.40	8.97
Starch	ND	NA	ND	NA
Flour	0.04	1.71	0.02	0.52
Grits	ND	NA	0.004	0.68
Crude Oil(2)	ND	NA	ND	NA
Refined Oil(2)	ND	NA	ND	NA
Meal	0.03	1.31	0.05	1.01

(1) Aspirated grain fractions
(2) Both wet and dry milled products

Copies of typical chromatograms, standards, and calibration curves are included in the submission.

Geographic Representation

The geographic diversity of the studies are inadequate to represent the U.S. field corn growing regions. Twenty successful field corn studies with the correct geographic diversity are required to support a permanent tolerance. The twelve residue studies

submitted here were located in Region 5 (11) and in Region 6 (1). This represents 86% of the domestic field corn growing regions. However due to the large acreage of domestic field corn production and the variability observed in the residues, eight more successful studies are necessary to establish a permanent tolerance: six more in Region 5 (midwest), one in Region 1 (northeast), and one in Region 2 (southeast).

Storage Stability

No storage stability data were included in this submission. Samples were stored frozen for a maximum of 315 days. The available storage stability data indicate that residues of glyphosate in or on plant commodities are stable if frozen for up to a period of 1 year (Residue Chemistry Chapter, 10/27/92). No additional storage stability data are required for this proposed use.

Meat, Milk, Poultry, and Eggs

Dietary Burden
Corn grain, forage, fodder, and aspirated grain fractions are animal feed items. Corn grain can be 80% of the diets of beef cattle, poultry, and swine and 40% of dairy cattle diets. Fodder can be 25 and 15% of the diets of beef and dairy cattle respectively. Aspirated grain fractions can be 20% of the diets of beef and dairy cattle and swine.

Table III: Maximum Dietary Burden of Glyphosate Residues in Field Corn Feedstock Items

Dietary Burden* Commodity	Beef Cattle ppm	Dairy Cattle ppm	Poultry ppm	Swine ppm
grain	0.6	0.05	0.9	0.9
fodder	30.1	18.1	NU	NU
aspirated grain fractions	47.1	47.1	NU	47.1

* Dietary Burden= % of diet x tolerance/% dry matter
NU Not significant dietary component
Highest glyphosate exposure is for beef cattle = 78 ppm based on 20% aspirated grain fractions, 25% corn fodder, and 55% grain.

Feeding Study
No feeding studies were submitted with this petition. Feeding studies have been conducted in which cattle, swine, and poultry were dosed with a (9:1) mixture of glyphosate and AMPA at 0, 40,

120, and 400 ppm for 28 days and then slaughtered. The results of the feeding studies are presented in Table IV. No residues were found in milk or fat at any dosing level. Only minimal residues were found in eggs and muscle at 400 ppm. Significant residue levels were found in animal liver and kidney at the 120 and 400 ppm levels (PP#6F3380/ FAP6H5502, DEB#s: 4285 and 4286, 1/30/89).

Table IV: Results of the Glyphosate Feeding Study

Feeding Level ppm Tissue	40	120	400
meat*	<0.05	<0.05	0.06
kidney			
cattle	0.26	1.00	4.10
swine	0.37	2.88	8.77
poultry	0.38	1.23	4.87
liver			
cattle	0.06	0.07	0.41
swine	<0.05	0.33	1.14
poultry	0.07	0.30	1.16
fat*	<0.05	<0.05	<0.05
eggs	<0.05	<0.05	0.10
milk	<0.05	<0.05	<0.05

* All animals.

Contribution of New Uses

Glyphosate tolerances for kidney and liver of cattle, goats, hogs, horses, poultry, and sheep are in the process of being raised to 4 ppm (PP#4F4312, M. Rodriguez, 1/11/95). The pending tolerances are for a preharvest use of glyphosate on alfalfa. Based on the above feeding study the addition of the dietary burden of at most 78 ppm glyphosate residues on corn commodities (Table III, beef cattle, if an all corn commodities diet were fed) will be covered by the pending tolerances in PP#4F4312. The secondary residues on cattle meat and milk are not expected to be a problem even if alfalfa hay is added to the diet (see Table V) provided the 4 ppm liver and kidney tolerances are established.

The use of corn commodities containing glyphosate residues as a feed for poultry would produce a burden of 0.9 ppm (Table III) which would produce non detectable residues (Table IV). Secondary residues on poultry and eggs are not expected to be a problem.

The use of corn commodities containing glyphosate residues as a

feed for swine would produce a burden of 48 ppm (Table III) which would produce residues (Table IV) well below the pending tolerances. Secondary residues on swine products are not expected to be a problem.

Table V: Worst Case Glyphosate Dietary Exposure For Beef Cattle

Feed Item	Tolerance ppm	% in Diet	% Dry Matter	Exposure ppm
aspirated grain fractions	200	20	85	47.06
corn fodder, field	100	10	83	12.1
alfalfa hay	200	70	89	157.30

Total exposure = 216.4 ppm.

Other Considerations

Codex MRL's, and Mexican limits on maize for the residues of glyphosate exist at 0.1 ppm. Canadian limits for the residues of glyphosate exist on 'all other food crops' exist at 0.1 ppm. In addition, a Codex MRL on the straw and fodder, dry of cereal grains for the residues of glyphosate exist at 100 ppm. The registrant should propose and support an increase in the Codex limit for maize to 1 ppm.

Attachment: International Residue Limit Status

cc: RF, PP#8F03673, circ., Cutchin, Ives
7509C: CBTS, Reviewer (WDC), CM#2, Rm 804P, 305-7990, WDC: 3/21/96
R/I: Br. Sr. Sci.: R. Loranger, 3/12/96;
Act. Br. Chief: R. Perfetti, 3/13/96

(12)

T. Koes
11/1/95

Attachment:

Page 1 of 1

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Glyphosate

CODEX NO. 158

CODEX STATUS:

[] No Codex Proposal Step 6 or Above

Residue (if Step 8): _____

Glyphosate

Crop(s)	Limit (mg/kg)
Maize	0.1 *
Straw & fodder dry of cereal grains	100

PROPOSED U.S. TOLERANCES:

Petition No. 8F3673

DEB Reviewer Cutchin

Residue: Glyphosate

Crop(s)	Limit (mg/kg)
Corn grain, field	1
Corn fodder, field	100
aspirated grain fractions	200
Corn milled byproducts, field	1

CANADIAN LIMITS:

[] No Canadian Limit

Residue: _____

Glyphosate

Crop(s)	Limit (mg/kg)
"all other food crops"	0.1 **

MEXICAN LIMITS:

[] No Mexican Limit

Residue: _____

Glyphosate

Crop(s)	Limit (mg/kg)
Maize	0.1

NOTES

* At or about the limit of determination

** Negligible residue type limit

Form Revised 1989