PM 15D/TSB

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

0266-A

NOV 4 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP#4F3127: Metsulfuron Methyl on Small Grain Cereals, Meat, and Milk. Amendments of 8/1/85 and 10/25/85.
RCB Numbers: 1323, 102
Accession Numbers: 073736, 073737

MRID 147506 - 147508

FROM: Karl H. Arne, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

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

TO: Robert Taylor, Vickie Walters, Team No. 25
Registration Division (TS-767)
and
Toxicology Branch
Hazard Evaluation Division (TS-769)

With this amendment the petitioner, Dupont, has responded to several deficiencies that were noted in RCB's original review (memo of 7/21/85, P.Errico). The deficiencies will be listed below, and each will be followed by the petitioner's response and RCB's comments. In the following discussions, several compounds are referred to by Dupont code numbers or other names. The structures of impurities in the technical material are given in Confidential Appendix A, and structures of metabolites are given in Appendix B.

Deficiency 1a:

Analysis of impurities in the technical material has been sent for only one lot-numbered sample. Analysis of impurities in the technical material should be submitted, at a minimum, on a total of five samples reflecting five different lot numbers.

Petitioner' Response:

The petitioner has submitted analyses of five batches. The [redacted] The analyses are detailed in Confidential Appendix A.

Information which may reveal the manufacturing process is not included.

RCB's Comment:

We do not expect the impurities to result in any residue problems. This deficiency is resolved.

Deficiency 1b:

The analysis of the petitioner's >93% technical material [redacted] The petitioner should clarify these results and submit a complete analysis of their >93% technical including quantitation of any impurities comprising >0.1%. If additional impurities are detected and they are not determined using the submitted methodology for enforcing ingredient limits, additional analytical methodology will be needed.

Petitioner's Response:

[redacted] excluded from the impurity profile. These compounds are included in the analyses discussed under 1a, above. In addition, Dupont has provided certified limits for these impurities. Enforcement methods for certification of limits are referenced. See Confidential Appendix A.

RCB's Comment:

This deficiency is resolved.

Deficiency 2a:

See Confidential appendix for a discussion [redacted]

Petitioner's Response:

See Confidential Appendix.

RCB's Comment:

This deficiency is resolved.

Deficiency 2b:

A current Confidential Statement of Formulation should be submitted to determine whether inerts are cleared under 40 CFR 180.1001.

Petitioner's Response:

The petitioner has submitted the requested Confidential Statement of Formula. See Confidential Appendix. All inerts in the formulation are cleared.

Information which may reveal the manufacturing process is not included.

RCB's Comment:

This deficiency is resolved. However, see 2a, above.

Deficiency 2c:

Permanent tolerances in barley and wheat have not been established for the active ingredients in Kerb and Chem HOE 135. These should be removed from the label as sequential or mixture candidates.

Petitioner's Response:

In the proposed labeling, Ally© is recommended for control of volunteer cereals and grassy weeds on fallow land in tank mix with Rohm and Haas Kerb© Herbicide and PPG Chem Hoe© 135 for use on fallow land. Labels for these herbicides have been submitted.

RCB's Comments:

The submitted labels show that Kerb and Hoe are registered for use on fallow land. This deficiency is resolved. RCB notes, however, that these fallow land uses were registered without our review. RCB earlier determined that, in the absence of radiolabel studies showing otherwise, the use of Hoe would not be considered a non-food use (see PP#8G2088, memo of 1/4/80, R. Hummel).

Deficiency 3:

No information on the fate of the triazine portion of the molecule has been submitted. The petitioner should submit a small grain metabolism study which depicts the fate of the triazine portion of the parent molecule. The triazine molecule should be 14C-labeled.

Petitioner's Response:

The petitioner has submitted a study entitled "Metabolism of [Triazine-2-14C] Metsulfuron Methyl in Greenhouse-Grown Wheat." A summary follows.

Greenhouse-grown wheat at the 3-5 leaf stage was treated at the rate of 1 oz. a.i./A with 14C-triazine ring labeled metsulfuron methyl (the proposed use calls for applications of 0.06-0.12 oz. a.i./A). Samples were collected immediately after application, one, two, and four weeks later, and at harvest, 9.3 weeks after application. The plants were kept frozen until analysis.

Dried samples were combusted and the evolved $^{14}CO_2$ determined by liquid scintillation counting (LSC). Residues in foliage (dry weight) were 8.2 ppm immediately after application and gradually decreased to 0.81 ppm four weeks later. At harvest (9.3 weeks), residues were 1.5 ppm in husks and 0.0082 ppm in grain.

Surface residues were removed by a methanol wash followed by a chloroform wash. The remaining plant tissue was extracted with 80% acetone in water. Cellular debris was separated then washed with the extraction solvent before combustion and LSC.

The acetone/water extract was reduced by rotary evaporation. Distilled water was added, the pH was adjusted to 10, and the resulting suspension was extracted with hexane. The pH of the water phase was lowered to 3.2 with phosphoric acid; this was then sequentially extracted with methylene chloride and n-butanol.

The two surface washes (methanol and chloroform) and the three extract fractions (methylene chloride, n-butanol, and water) were reduced to dryness by rotary evaporation. The residues from the methanol wash, the n-butanol fraction, and the water fraction were redissolved in chloroform, and the methylene chloride fraction was redissolved in methylene chloride. Samples of each fraction were subjected to TLC for identification of metabolites by comparison to known standards.

The activity in the various fractions was distributed as shown in the following table

	Percent of Total Radioactivity in Indicated Fraction						
PHI	Surface Wash			Cell interior			Unextracted
(Days)	Methanol	$CHCl_3$	n-hexane	CH_2Cl_2	n-butanol	H_2O	Bound
0	46	14	0.3	37	1.7	0.5	0.5
7	49	13	0.2	32	2.6	0.8	2.9
14	31	11	0.1	47	5.8	1.0	3.4
28	35	13	0.3	29	14	7	2.1
65	30	12	0.3	24	13	8	6.7

Results of TLC identification are described in the following table:

	PPM Metsulfuron Methyl Equivalents				
Compound	0 day	7 days	14 days	28 days	65 days
Metsulfuron Methyl	1.65	0.74	0.66	0.24	0.44
Metabolite A1	0.01	0.03	0.03	0.05	0.08
Triazine aminel	0.04	0.01	0.02	0.02	0.09
Hydroxymethyl triazine aminel	<0.01	<0.01	0.01	<0.01	0.02
Hydroxymethyl metsulfuronl	0.12	0.04	0.03	0.02	0.05
Metabolite A11	0.03	0.01	0.01	0.01	0.04
Polar 1	0.02	0.01	0.01	0.02	0.07
Polar 2	0.01	0.01	0.01	0.01	0.06
Unidentified2	0.02	0.01	0.03	0.01	0.05
n-hexane extractable	0.01	<0.01	<0.01	<0.01	<0.01
Unextracted	0.01	0.03	0.03	<0.01	0.07
Total	1.92	0.89	0.84	0.38	0.98

1-Structures are given in Appendix B
2-Unidentified activity distributed over TLC plates

RCB's Comment's:

This study corroborates the previously submitted studies that used 14C-phenyl ring-labeled metsulfuron methyl (see PP#3G2834, memo of 4/13/83, J. Worthington, and the 1/21/85 P. Errico memo to the subject petition). The relative proportion of metabolites is different, but the results are qualitatively similar. Two metabolites that were not uncovered in the previous studies (because label placement would not allow it), triazine amine and hydroxymethyl triazine amine, were uncovered at maximum levels of 9 and 2%, respectively, in the most recent study.

RCB concludes that, for the purpose of the proposed uses on cereal grains, the nature of the residue is adequately understood. The residues of concern consist of metsulfuron methyl and its metabolites methyl 2-[[[[(4-methoxy-6-methyltriazine2-yl)amino]-carbonyl]amino]sulfonyl-4-beta-D-glucopyranosylbenzoate (metabolite A) and methyl 2-[[[[(4-methoxy-6-methyltrizaine-2-yl)amino]carbonyl]amino]sulfonyl]-4-hydroxybenzoate (metabolite A1). However, any future use that reults in higher residues on any crop may trigger the need for more complete identification of residues.

Deficiency 4a:

In plants treated with [14C-phenyl] metsulfuron methyl, terminal residues reported are parent compound, metabolite A (glucose conjugate of metabolite A1), and metabolites A1, I, II, III, and saccharin. RCB will reserve its recommendation for the tolerance expression until the fate of the triazine moiety is determined after reviewing the triazine study requested with deficiency 3, above.

Petitioner's Response:

No comment.

RCB's Comment:

This deficiency is resolved. See RCB's comments under deficiency no. 3, above.

Deficiency 4b:

From 23 to 65% of the terminal residues in small grain forage were not identified in the submitted plant metabolism studies. These radiolabel metabolites should be identified. Alternatively, assuming no problems with the requested storage stability (see No. 11, below) and the triazine metabolism study (No. 3, above). we could conclude that the nature of the residue in plants is understood for the proposed use if the petitioner submits a revised Section B which includes a restriction against grazing livestock or harvesting forage or hay until 28 days after treatment.

Petitioner's Response:

As indicated in the table below (prepared from the data in the greenhouse wheat metabolism study), the actual concentration of these radiolabeled residues is extremely small.

"COMPOUND"	PPM UNIDENTIFIED ACTIVITY				
	1-Week	2-Weeks	4-Weeks	Mature Straw	Mature grain
oz a.i./A					
Nonpolar	0.07	0.1	0.07	<0.01	<0.01
Unidentified	<0.01	0.08	<0.01	0.03	<0.01
Polars	0.37	0.57	0.22	0.03	<0.01
oz a.i./A					
Nonpolar	0.18	0.07	<0.01	<0.01	<0.01
Unidentified	0.10	0.03	<0.01	0.06	0.02
Polars	0.14	0.13	0.17	0.01	<0.01

The "nonpolar" unknown (R_f = 0.95) occurs mainly as a surface residue and becomes increasingly small with time.

The unidentified unkowns consist of at least four compounds having R_f values of 0.29, 0.44, 0.51 and 0.88. The compound migrating with an R_f of 0.44 is probably "hydroxymethyl metsulfuron methyl," just recently discovered in the [triazine-2-14C] metsulfuron methyl study. This compound had not been synthesized when the original studies were in progress.

The "polar" activity (R_f = 0.0), which comprises the greatest percentage of unkowns, are probably more highly metabolized compounds which can eventually become incorporated into the plant as unextractable residues (D. Penner, Metabolism of Herbicides in Higher Plants, Burgess, Minneapolis MN, 1982, Chapter 3). Characterization and identification of these polar residues are normally much more difficult. Like the other unkowns the concentration of polars becomes insignificantly small with time.

As indicated in the table below (prepared from data in the field wheat study, the field barley study, and the recent greenhouse wheat study), the percentage of characterized radioactivity is consistently very high.

	PERCENT OF IDENTIFIED TOTAL RADIOACTIVITY IN SAMPLE*			
	0-Week	1-Week	2-Week	4-Week
Field Wheat	93	83	86	73
Field Barley	97	92	72	75
Greenhouse Wheat	97	97	94	89

*Data for the two field studies were calculated by subtracting the total characterized and unextracted radioactivity from the total radiolabel residues. Data for the greenhouse study was calculated by subtracting the percent unkowns from from 100%.

Like the original greenhouse wheat study, the concentration of unidentified activiey in these studies is extremely low.

	PPM OF UNIDENTIFIED TOTAL RADIOACTIVITY IN SAMPLE*			
	0-Week	1-Week	2-Week	4-Week
Field Wheat	0.12	0.12	0.12	0.12
Field Barley	0.08	0.07	0.20	0.05
Greenhouse Wheat	0.06	0.03	0.05	0.4

RCB's Comment:

The percent of identified residues in the three studies discussed above ranges from 75-94% at two to four weeks after harvest. The 23-65% unidentified activity at these same time intervals was from an earlier greenhouse wheat metabolism study.

The available cereal metabolism studies show a varying percentage of unidentified activity. As expected, the proportion of unidentified activity increases with time as the absolute level goes down. In the most recent study, the residue at the time of the season which wheat or barley could be used for forage is well characterized. RCB concludes that the nature of the residue in wheat and barley forage is adquately understood and that, for the purposes of the proposed use, no further identification is necessary. Any future use that may result in higher residues could trigger a requirement for further identification of activity.

Deficiency 5:

In the rat metabolism study, the term "carcass" was used to define the rat material analyzed. The petitioner should describe what the "carcass" consists of in their analysis.

Petitioner's Response:

In the rat metabolism study, the term "carcass" is the residual muscle, skin, and bone after all the internal organs have been removed.

RCB's Comment:

This information helps to better define the rat metabolism study (See P. Errico memo of 7/21/85). The rat metabolism study in not essential, however, but complementary to metabolism studies on food animals. This deficiency is resolved.

Deficiency 6

In "Metabolism of the 14C-Metsulfuron Methyl Wheat Metabolite A in a Goat," no explanation was given for how the reported radiochemical purity of 14C-labeled metabolite was determined.

The goat was reportedly fed at a dietary rate of 38 ppm Metabolite A. This figure (38 ppm) could not be recalculated using the data submitted in the study. The petitioner should explain how the reported radiochemical purity of Metabolite A was determined and how the dietary feed rate of 38 ppm equivalent Metabolite A was calculated.

Petitioners Response:

In the goat metabolism study, the radiochemical purity and dietary feed rate were determined as follows.

A 10.0 mg aliquot of the lyophilized wheat metabolites was dissolved in water whose pH has been adjusted to 2.2 with phosphoric acid. The resulting aqueous solution was sequentially extracted with methylene chloride and n-butanol. The total radioactivity in each fraction was determined by liquid scintillation counting. Each fraction was concentrated, first on a rotary evaporator, then under a stream of nitrogen, to a final volume of 1 mL. Aliqouts of each were applied to 0.25 mm silica gel thin-layer chromatography plates, and the plates were developed to 15 cm with methylene chloride/methanol/concentrated ammonium hydroxide (144/50/6, v/v/v). Autoradiograms of the developed plates were prepared using Kodak SB-5 X-ray film. Radioactive areas on each plate were mixed with 3.5 mL of water and 11.5 mL of Formula 947 Liquid Scintillation Cocktail (New England Nuclear), and the total radioactivity of each solution was counted on a TM Analytial Mark III LSC Spectrometer. The dpm of the Metabolite A fraction (R_f = 0.10) on each developed plated was divided by 100% to obtain the percent metabolite A in each fraction. Each of these percentages was multiplied by the fraction of total radioactivity in that extract. The resulting percentages for each fraction were added to give the total radiochemical purity. Sentence 3 of the "Dosing" section (on Page 3 of Document No. AMR-156-83) is incorrect and should read: "The goat was dosed with a gelatin capsule containing 3.4 g of wheat extract which is equivalent to 17 ppm of metsulfuron methyl wheat metabolite A in the daily diet." As indicated on page 3, each dose contained 38.7 mg (0.0387 g) of total radiolabeled compounds, 45% (0.45) of which was wheat metabolite A. Assuming a 1 Kg (1000 g) average daily feed intake, one can calculatee the daily dietary feed rate of wheat metabolite A:

$$\frac{(0.0387g)\ (0.45)\ (10^6)}{1000\ g} = 17\ ppm$$

RCB's Comment:

This deficiency is resolved.

Deficiency 7

No representative chromatograms for control and metsulfuron methyl fortified barley grain and green forage were submitted for the methods described in report AM-104-82. These chromatograms

should be submitted for our perusal.

Petitioner's Response:

Representative chromatograms have been submitted.

RCB's Comment:

The submitted chromatograms support the claimed sensitivity of 0.02 ppm for grain and forage and a sensitivity of 0.05 for straw. This deficiency is resolved.

Deficiency 7b:

Assuming no problems are identified with the above requested sample chromatograms for barley grain, straw, and green forage, the submitted methodology which determines metsulfuron methyl in barley and wheat plant material appears adequate as an enforcement method. Submitted analytical methodology for meat and milk also appear adequate. Our final conclusions on the use of these methods for enforcement will depend on the results of a method try-out.

Petitioner's Response:

None.

RCB's Comment:

See No. 7a, above and 7c, following.

Deficiency 7c:

Before a method try-out can be requested, the petitioner must submit clean copies of the methodology for wheat, barley, meat, and milk without the confidential and "not for publication" labels.

Petitioner's Response:

The petitioner has submitted clean copies of the following methods: "Determination of Metsulfuron Methyl in Crops by Liquid Chromatography," "Determination of Metsulfuron Methyl Metabolite A and Metabolite Al in Cereal Grains by Liquid Chromatography," and "Determination of Metsulfuron Methyl Residues in Bovine Samples."

RCB's Comment:

This deficiency is resolved. A method trial has been requested (see memo of, 11/1/85, K. Arne).

Deficiency 8:

In Table 3 (Recovery Data) in the report "Determination of Residues of Metsulfuron Methyl Metabolte A by Liquid Chromatography," the recovery range for barley forage was reported as 0-90% with an average of 80%. The petitioner should verify that 0-90% is a typo and give the correct recovery range for these samples.

Petitioner's Response:

The recovery range should have been reported as 70-90% with an average recovery of 80%.

RCB's Comment:

This deficiency is resolved.

Deficiency 9a:

The equation used to calculate the sample concentration of Metabolite A contains the correction factor Pc, which depends on the availability of untreated control samples. Because pesticide enforcement officials usually do not have access to known untreated control samples, we cannot accept analytical methodology for enforcement purposes which require corrections for interfering plant constituents. The petitioner should modify the proposed enforcement method for Metabolite A so this correction factor is not necessary.

Petitioner's Response:

The purpose of the Pc factor is to correct for any crop interferences which may occur in a set of samples. If a control is not available this correction cannot be made to samples. Normally this is not a problem. Therefore the method has been revised and the Pc factor eliminated.

RCB's Comment:

This deficiency is resolved.

Deficiency 9b:

It cannot be discerned from the grain data whether free Metabolite Al is determined with the conjugated Metabolite A in the analytical method for Metabolite A. The petitioner should verify that the enforcement method submitted for Metabolite A also determines any free Metabolite Al; otherwise the method should be modified so Metabolite Al is determined. Validation data for Metabolite Al should also be submitted.

Petitioner's Response:

The revised method determines both Metabolite A and Metabolite Al. Recoveries are summarized in the following table.

	Recovery of Metabolite A1			Recovery of Metabolite A		
	fort.(ppm)	range(%)	average	fort.(ppm)	range(%)	average
barley grain	0.02-0.2	85-94	90	0.03-0.2	88-103	94
barley straw	0.05-0.5	69-84	79	0.075-0.5	73-91	82
wheat forage	0.04-0.4	75-95	86	0.06-0.5	86-95	89
wheat grain	0.02-0.2	75-91	86	0.03-0.2	88-96	92
wheat straw	0.05-0.5	61-78	73			

RCB's Comment:

These are adequate recoveries. This deficiency is resolved.

Deficiency 10a:

The petitioner should state whether all beta-glucosidases or only type II beta-glucosidase from almonds give satisfactory results in the enzymatic hydrolysis step in the analytical method for Metabolite A.

Petitioner's Response:

The Type II beta-glucosidase from almonds used is a commonly used enzyme, readily available from commercial sources. The use of other beta-glucosidases would probably also work, but the percent reaction would have to be checked as described in the procedure.

RCB's Comment:

This deficiency is resolved.

Deficiency 10b:

Assuming the method can be satisfactorily modified per 9a and 9b and before we can request a method try-out for the Metabolite A, analytical methodology using an enzymatic hydrolysis, the petitioner should show that acid or base hydrolysis is not adequate.

Petitioner's Response:

The sulfonylurea moiety is sensitive to hydrolysis by both acid and base as illustrated in the hydrolysis studies submitted by Dupont. Therefore, attempts to hydrolyze the glucose linkage by either acid or base would undoubtedly result in destruction of the basic molecule into smaller units which would be much more difficult to analyze for.

RCB's Comment:

The hydrolysis report shows that metsulfuron methyl is susceptible to acidic hydrolysis (pH=2) even at room temperature. At pH=9 it is relatively stable at 45° ($t_{1/2}$=260 hours); more basic conditions were not used in the hydrolysis studies. However, we do not expect the glucose linkage, an acetal, to be

susceptible to basic hydrolysis. RCB accepts the petitioner's argument that neither acid or base hydrolysis would be useful for glucose cleavage. This deficiency is resolved.

Deficiency 10c:

The enforcement methods proposed for Metabolite A are marked confidential. We will need clean copies of these methods without the confidential label before requesting a method try-out.

Petitioner's Reponse:

The petitioner has submitted clean copies of "Determination of Metsulfuron Methyl in Crops by Liquid Chromatography" and "Determination of Metsulfuron Methyl Metabolite A and Metabolite A1 in Cereal Grains by Liquid Chromotography."

RCB's Comment:

This deficiency is resolved. However, see 7c, above.

Deficiency 11:

No storage stability studies on raw residue data were submitted. The petitioner was informed in our review of PP#3G2834 (memo of 4/13/83, J. Worthington) that these data should be provided in the permanent tolerance request. These should be submitted.

Petitioner's Response:

A storage stability study, including sample chromatorgams, has been submitted. Wheat was spiked with metsulfuron methyl at 100 ppb and analyzed after 1, 3, 6, 12, 19, 24, and 36 months of frozen storage (recoveries immediately after spiking were 83-91%). There was no apparent degradation. Recoveries at 36 months ranged from 86 to 91% and were typical of those for the whole experiment. Recoveries from wheat forage and straw fortified at 100 ppb gave somewhat lower (54-79%) recoveries after 12 months frozen storage. For the forage and straw samples recoveries immediately after spiking were 74-88%.

RCB's Comment:

These recoveries are adequate. This deficiency is resolved.

Deficiency 12a:

In the study entitled "Fate of Metsulfuron Methyl Ingested by Dairy Cows," mash was fortified with metsulfuron methyl. The validated methodology and sample chromatograms should be submitted for the fortified mash used in this cow study.

Petitioner's Response:

The petitioner has revised this report to include an appendix that explains the procedure for analysis of feed mash and includes validated methodology and sample chromatograms.

RCB's Comment:

This deficiency is resolved. The procedures for analysis and validation and the sample chromatograms are adequate.

Deficiency 12b:

In the text of the cow feeding study (see 12a, above), analyses of liver sampes were reported, and a sample chromatogram for this tissue was submitted. However the results of these analyses were not reported. The petitioner should submit these missing data.

Petitioner's Response:

This study has been revised to include results of liver analyses. Of the three levels fed (5, 20, and 100 ppm) only the highest level resulted in detectable residues (75 ppb) in liver.

RCB's Comment:

This deficiency is resolved.

Deficiency 12c:

In this same dairy cow feeding study, figure 9 relates to kidney sample of cow #7 containing 0.67 ppm metsulfuron methyl. This residue in the kidney of cow #7 is reported as 0.12 ppm in table 10. The petitioner should explain this discrepancy.

Petitioner's Response:

The kidneys were analyzed twice. Variability in the results was apparently due to different levels of urine in the kidney samples. The report has been revised to include only one set of analyses. Table 10 and figure 9 now both report the level of metsulfuron methyl in kidneys to be 0.67 ppm.

RCB's Comment:

This deficiency is resolved.

Deficiency 13b:

Residue data reflecting exaggerated use rates of up to 4X lead to no detectable residues of parent and Metabolite A in wheat grain. However, we withhold our final conclusion on the necessity for wheat and barley milling studies until the requested

data on the fate of the triazine moiety in plants has been submitted and reviewed, and the storage stability question in Conclusion 11 is satisfactorily resolved.

Petitioners Response:

No comment.

RCB's Comment:

Plant metabolism questions have been resolved (see 3 and 4a, above) and questions about storage stability have been resolved (see 11, above). This deficiency is resolved. Milling studies are not required.

Deficiency 13c

No residue data were submitted for wheat and barley hay. The petitioner should submit residue data and propose tolerances for these RAC's. Alternatively, the petitioner can propose tolerances by calculating exposure using the dry-down factor of 4.

Petitioner's Response:

The petitioner wishes to propose tolerances fpr wheat and barley hay using a dry-down factor of 4. A revised Section F in which tolerances of 20 ppm are proposed has been submitted.

RCB's Comment:

This deficiency is resolved. The tolerance level for wheat and barley forage is 5 ppm.

Deficiency 14a:

Assuming no additional toxic residues of concern in plants are found and the questions in 12b and 12c are answered satisfactorily, we can conclude for the purposes of the proposed use that the nature of the residues in animals is adequately understood. The residue of concern in meat and milk consists of the parent compound, metsulfuron methyl.

Petitioner's Response:

No comment.

RCB's Comments:

No additional toxic residues of concern in plants have been uncovered, and deficiencies 12b and 12c have been resolved. Deficiency 14a is resolved.

Deficiency 14c:

With a restriction against harvesting small grains as hay and assuming satisfactory answers to the triazine moiety question in plants, for this use we can tentatively recommend for the requested tolerance of 0.05 ppm in milk and 0.1 ppm in meat (except liver and kidney), fat, and meat byproducts. We withhold our recommendation on tolerances for kidney and liver until we have received the requested information from Conclusion 12b and c above.

Petitioner's Response:

No comment.

RCB's Comment:

Since we now consider the nature of the residue in forage to be adequately understood (see 4b, above) and since deficiencies 12b and 12 c are resolved, we can recommend for the proposed tolerances in milk (0.05 ppm) and meat (0.1 ppm). This deficiency is resolved; feeding and grazing restrictions are not required.

Other Considerations:

The petitioner has proposed tolerances of 0.1 ppm for meat, fat, and meat by-products (except liver and kidney) and tolerances of 0.1 ppm for liver and kidney. Since the tolerance levels are the same, it isn't necessary to separate liver and kidney. A tolerance of 0.1 ppm for the meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep should be proposed.

Also, the tolerance expression for crops should be expressed in terms of metsulfuron methyl and its metabolite, methyl 2-[[[[(4-methoxy-6methyl-1,3,5triazin-2-yl)amino]sulfonyl]-4-hydroxybenzoate. For meat and milk, the tolerance should be expressed in terms of metsulfuron methyl only. This will require two sections for the tolerance expressions, one for crops and one for meat, milk, poultry and eggs.

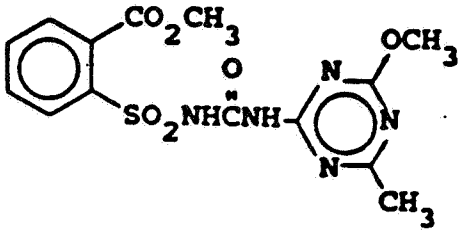
Recommendations

RCB recommends against the proposed tolerance. For further consideration the petitioner should revise Section F as outlined under Other Considerations, above. Also, a favorable recommendation is contigent on the successful completion of a method trial as requested in our 11/1/85 memo to COB.

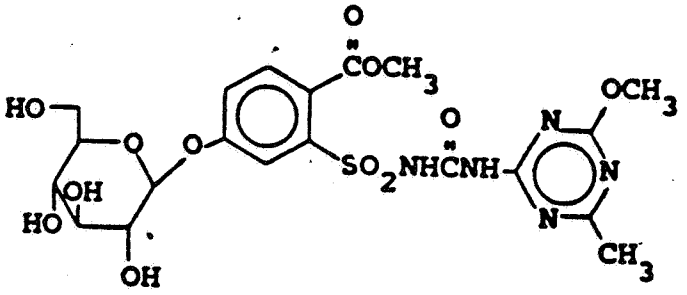
Attachment 1: Confidential Appendix A (4 pages),(copies to TOX, RD PM, RF, Reviewer, PP#4F3127, PMSD/ISB)
Attachment 2: Appendix B (copies to all addressees and to all cc'd)
cc: TOX, RD PM, Reviewer, PP#4F3127, PMSD/ISB, Circ., EEB, EAB, FDA, RDI: PVE, 10/31/85; RDS, 10/31/85

APPENDIX B
RCB No. 1323
Page 1 of 2

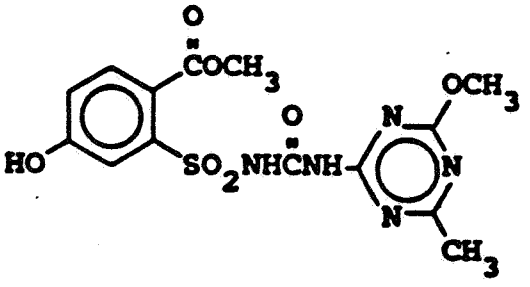
STRUCTURES AND CHEMICAL ABSTRACTS NAME OF METSULFURON METHYL AND RADIOLABEL METABOLITES



Metsulfuron Methyl (DPX-T6376, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]sulfonyl]benzoic acid, methyl ester

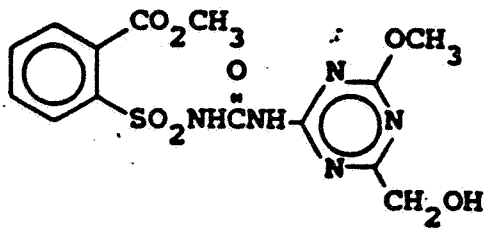


Metabolite A (Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5triazin-2-yl)-amino]sulfonyl]-4-beta-D-glucopyranosylbenzoate

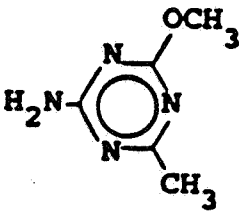


Metabolite A1 (Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5triazin-2-yl)-amino]sulfonyl]-4-hydroxybenzoate

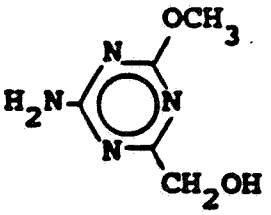
APPENDIX B
RCB No. 1323
Page 2 of 2



Hydroxymethyl Metsulfuron Methyl (DPX-T6376, 2-[[[[(4-methoxy-6-methyl-1,3,5triazin-2-yl)amino]sulfonyl]benzoic acid, methyl ester)



Triazine amine (4-methoxy-6-methyl-1,3,5triazin-2-amine)



Hydroxymethyl triazine amine (4-methoxy-6-hydroxymethyl-1,3,5-triazin-2-amine)

Pages 22 through 25 contain information on the product quality control procedures. These pages are not included.