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

JUN 21 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#4F3127 Metsulfuron Methyl Use on Small Grain Cereals, Meat and Milk. Evaluation of Analytical Methods and Residue Data (Accession Nos. 072767 and 072768). [RCB#87].

FROM: Philip Errico, Chemist
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THRU: Charles L. Trichilo, Ph.D., Chief
Residue Chemistry Branch
Hazard Evaluation DIvision (TS-769)

TO: Robert Taylor/Vicki Walters, PM25
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division(TS-769)

The E. I. DuPont de Nemours and Company has requested tolerances for metsulfuron methyl (methyl-2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate; (formerly DPX-T6376) in/on:

Commodity	ppm
wheat grain	0.05
wheat straw	0.1
wheat green forage	5.0
barley grain	0.05
barley straw	0.1
barley green forage	5.0
milk	0.05
meat, fat, and meat by-products (except kidney and liver) of cattle, goats, hogs, horses, and sheep	0.1
kidney and liver of cattle, goats, hogs, horses, and sheep	0.1

Conclusions

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.

1b. The analysis of the petitioner's >93% technical chemical includes [redacted] reported in PP#3G2834, but these impurities are not mentioned in this petition. The petitioner should clarify these results and submit a complete analysis of their >93% technical and included unintentional impurities >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.

Information which may reveal the manufacturing process is not included.

2a. See Confidential Appendix for a discussion of an [redacted]

2b. A current Confidential Statement of Formulation should be submitted for Ally® dry flowable (60%) so all inerts can be evaluated under 40 CFR 180.1001 to determine whether they are cleared for use as inerts.

2c. Permanent tolerances in barley and wheat have not been established for the active ingredients in Kerb and Chem Hoe 135. Those should be removed from the label as sequential or mixture candidates.

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

4a. In plants treated with [^{14}C-phenyl] metsulfuran methyl, terminal residues reported are parent compound and the major catabolite, metabolite A (glucose conjugate of metabolite A1), and metabolites, A1, I, II, III, and saccharin (see metabolic pathway scheme in appendix). RCB will reserve its recommendation for the tolerance expression until the fate of the triazine moiety is determined after reviewing the triazine study requested in conclusion 3 above.

4b. From 23% to 65% of the terminal residues in small grain forage were not identified in the submitted plant metabolism studies. These radiolabeled metabolites should be identified. Alternatively, assuming no problems with the request storage stability (see Conclusion 11 below) and triazine metabolism studies, we could conclude the nature of the residue in plants is understood for this 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.

5. In the rat metabolism study Doc. No AMR-108-83, the term "carcass" was used to define rat material analyzed. The petitioner should describe what "carcass" consists of in their analysis.

6. In "Metabolism of the ^{14}C-Metsulfuron Methyl Wheat Metabolite A in a Goat, Doc. No. AMR-156-83" no explanation was given for how the reported radiochemical purity of 14C-labeled metabolite A was determined.

   The goat was reportedly fed at a dietary rate of 38 ppm Metabolite A. The 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.

7a. No representive chromatograms for control and metsulfuron methyl fortified barley grain and green forage were submitted for the methods described in reports AMR-104-82. These chromatograms should be submitted for our perusal.

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 purposes will depend on the results of a method-try-out.

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.

8. In Table 3 "Recovery Data" the report "Determination of Residues of Metsulfuron Methyl Metabolite A by Liquid Chromatography" by L. N. Hershberger (Doc. No. AMR-238-84), barley green forage has a reported recovery range of 0-90% and an average recovery of 80%. The petitioner should verify that 0-90% is a typo and give the correct recovery range for these samples.

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.

9b. It cannot be discerned from the grain data whether free Metabolite A1 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 A1; otherwise the method should be modified so Metabolite A1 is determined. Validation data for Metabolite A1 should also be submitted.

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.

10b. Assuming the method can be satisfactorily modified per 9a and 9b and before we request a method-try-out for the Metabolite A analytical methodology using an enzymatic hydrolysis step, the petitioner should show that acid or base hydrolysis is not adequate.

10c. The enforcement methods proposed for Metabolite A are marked Confidential. We will also need clean copies of these methods without the Confidential label before requesting method-try-outs.

11. No storage stability studies on raw residue data was submitted in this submission. The petitioner was informed in our review of PP#3G2834 (J. Worthington, April 13, 1983) that these data should be provided in the permanent tolerance request. We continue to request the submission of storage stability data and raw residue data (including chromatograms).

12a. In the study titled, Fate of Metsulfuron Methyl Ingested by Dairy Cows", L. W. Hershberger and D. W. Moore, II, Doc. No. AMR-167-83, mash was fortified with metsulfuron methyl. The validated methodology and sample chromatograms should be submitted for the fortified mash used in this cow study.

12b. In the text of the above mentioned cow feeding study, analysis of liver samples 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.

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 discrepacy.

13a. Assuming the plant metabolism study requested above to determine the fate of the triazine moiety (using ^{14}C-triazine) of metsulfuron methyl indicates that no new metabolites in need of regulations are found, no additional residue data is necessary. The proposed tolerance should not be exceeded under the proposed use pattern.

13b. Residue data reflecting exaggerated use rates of up to 4 X lead to no detectable residues of parent or its catabolite, 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 noted in Conclusion 11 above is satisfactorily resolved.

13c. No residue data was 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.

14a. Assuming no additional toxic residues of concern in plants are found and the questions in conclusions 12b and 12c above are answered satisfactorily, we can conclude for this proposed use, that the residue of concern for meat and milk is the parent compound, metsulfuron methyl.

14b. No poultry metabolism or feeding studies were submitted. These may be needed if future tolerane requests show significant residues in poultry feed items.

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 tolerances of 0.05 ppm in milk, and 0.1 ppm in meat (except kidney and liver), fat and meat byproducts. We withhold our recommendation on tolerances for kidney and liver until we have received and reviewed the requested information from Conclusions 12b & c above.

15. The attached International Residue Limit Status sheet shows no established foreign tolerances for this chemical; there will be no compatibility problem.

Recommendation

We recommend against the requested tolerances for the reasons cited in conclusions 1a,1b,2a,2b,2c,3,4,5,6,7a,7b,7c,8,9a,9b, 10a,10b,10c,11,12a,12b,12c,13b,13c,14a and 14b.

Various recropping intervals ranging from 4 to 48 months or more are recommended in Section B depending on the application rate and use pattern. We defer to EAB as to the need for crop rotation restriction and/or whether rotational crop tolerances are necessary.

Detailed Considerations

Manufacturing Process - See Confidential Appendix.

Formulation - See Confidential Appendix.

Proposed Use

In spring or winter wheat or barley after the 2 to 3 leaf stage and before boot stage apply 0.06 oz.-0.12 oz. a.i./A. Apply postemergent when broadleaf weeds are less than 2 inches tall or in diameter and when crop canopy will not prevent thorough coverage of target weeds. Always include a surfactant. Do not use less than 0.06 oz a.i./A. If grass control is desired in addition to listed broadleaf weeds, use metsulfuron methyl with a suitable registered product. Use in 3 to 20 gallons of spray volume/Acre (GPA) for ground application or 1 GPA (use a minimum of 3 GPA by air in Idaho, Oregon, Utah and Washington) by air. In the event weeds are stressed by drought and/or cold temperatures, or crop canopy will prevent thorough coverage, use the higher recommended rates. The proposed use contains a built-in PHI of 25-40 days for grain and straw. However, there is no PHI for the wheat and barley forage.

There is also a proposed use in "reduce-tillage fallow weed control". For fallow application use 0.12 oz to 0.36 oz a.i./A. A restriction on p.4 of this submission allows only 0.36 oz a.i. per acre per 10 month period, but under PRECAUTIONS on p.8, no more than 0.36 oz. a.i. is allowed per year. The petitioner should make this restriction consistent throughout the proposed label. Volume of spray is the same as discussed under the post-plant use above.

Minimum recropping intervals are also recomended for both post plant and fallow uses. These intervals range from 4 to 48 months or more depending on application rate and use pattern. We defer to EAB as to whether crop rotation and/or rotational crop tolerances are necessary.

Tank mixes or sequential treatments are also proposed using metsulfuron methyl plus Roundup atrazine, Bladex, Igran, Kerb, Chem Hoe 135, Lexone DF, 2,4-D, Banvel or other suitably registered herbicide.

There are permanent tolerances established for the active ingredients in Roundup (glyphosate) in/on grain crops and forage grasses, in atrazine in/on wheat fodder, grain and straw, in Bladex (2-(4-chloro-6-ethyl-amino-s-triazin-2-ylamino)-2-methylpropionitrile in/on wheat forage (green), grain and straw, in Igran (terbutryn) in/on wheat and barley fodder, grain, green (sic) and straw, in Lexone DF [4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one] in/on barley grain and straw and wheat grain, forage and straw, and grass hay, in 2,4-D in/on barley and wheat forage and grain, and grass hay, and in Banvel (dicamba) in/on barley and wheat grain and straw, and grass hay. There are enforcement methodologies to support these tolerances in barley and wheat.

Permanent tolerances in barley and wheat have not been established for the active ingredients in Kerb [3,5-dichloro-N-(1,1-dimethyl-2-propynyl) benzamide] and Chem Hoe 135 (isopropylcarbanilate, propham). These should be removed from the label.

Nature of Residue

Several plant and animal metabolism studies have been submitted to support these proposed permanent tolerance requests. The study, "Metabolism of [^{14}C] DPX-T6376 in Greenhouse-Grown Wheat", J. J. Anderson (Doc. No. AMR-106-83), has been previously reviewed and the conclusions of the review are incorporated in the summary of this section (J. M. Worthington, PP#3G2834, April 13, 1983). The remaining submitted studies will be reviewed in turn.

Plant Metabolism

In study titled "Metabolism of [^{14}C] metsulfuron Methyl in Field-Grown Barley", J. J. Anderson (Doc. No. AMR-211-84), [^{14}C-phenyl] metsulfuron methyl was applied foliarly to barley in the tiller stage at the rate of 0.5 oz/A. The labeled compound was in a solution of water/methanol/DuPont surfactant WK® (90/10/0.25, v/v/v). Samples were taken at 0 time (after spray solution dried on leaf surface), then 1,2,4 and 9 weeks (maturity). Samples were freezed dried before storing at -20°C. Before solvent extraction a small amount of sample was combusted for total radioactivity. Grain and straw were analyzed as separate samples. All samples were extracted with 80% acetone/20% water (straw was extracted three times). Up to 92-96%, 71% and 52% of the activity was extracted from the immature foliage, mature grain and straw, respectively. Extraction of the straw sample with 0.01 M potassium phosphate buffer (pH 6.0) eluted another 15% of the total radioactivity. The remaining 4-8%, 33% and 29% of the radionuclide was reported as unextracted in foliage, mature straw and mature grain samples, respectively.

The extracts were concentrated to near dryness, diluted with water, and the pH adjusted to 3 with 1.0 M phosphoric acid. The aqueous solution was extracted 3-times each with methylene chloride and n-butanol. All extracts (aqueous, methylene chloride and n-butanol) were concentrated and the residues dissolved in methylene chloride (residues from the above methylene chloride extraction) or methanol (n-butanol and water fractions). Fractions worked up from straw and foliar samples were analyzed using thin layer chromatography (TLC); Extracts of the grain samples were analyzed using reverse-phase high pressure liquid chromatography (HPLC). Radioactive compounds separated by TLC or HPLC were identified using reference standards.

The petitioner reported the radionuclide decreased from 2.29 ppm at 0 time on foliage to 0.22 ppm in mature straw and 0.03 ppm in mature grain. The major residues extracted in methylene chloride was metsulfuron methyl and the minor metabolites, methyl 2-[[[[(4-methoxy-6-methyltriazin-2-yl)amino]sulfonyl]-4-hydroxybenzoate (metabolite A1) and methyl 2-(aminosulfonyl) benzoate (metabolite I). In n-butanol, the major metabolite identified was methyl 2-[[[[(4-methoxy-6-methyltriazin-2-yl) amino]-carbonyl]amino]sulfonyl]-4-beta-D-glucopyranosylbenzoate (metabolite A). Both the water and n-butanol fractions reportedly contained metabolites, Metabolite I, 2-(aminosulfonyl) benzoic acid (Metabolite II), saccharin, and methyl 2-(aminosulfonyl)-4-hydroxybenzoate (metabolite B). The percentage of total radionuclide identified was calculated as follows:

Sample Time (week)	Total Equivalent metsulfuron methyl ppm	% of Total Equivalent ^{14}C Metsulfuron Methyl								
		metsulfuron methyl	Metab. A	Metab. A1	Metab. B	Metab. I	Metab. II	Saccharin	Total Identified	Total Unidentified
0	2.29	83.4	1.8	2.6	<1	1.8		1.3	90.9	9.1
1	0.86	46.5	25.6	5.8	2.3	1.2	2.3	2.3	86.0	14.0
2	0.71	25.4	31.0	7.0	2.8	(a)	(a)	1.4	67.6	32.4
4	0.32	9.4	53.1	6.3	(a)	(a)	(a)	6.3	75.1	24.9
9 (straw)	0.22	(b)	9.1	9.1	(a)	(a)	(a)	4.5	22.7	77.3
9 (grain)	0.03	(a)	(a)	(a)	(a)	(a)	(a)	(a)		

(a) Not detected within limits of method sensitivity (<0.01 ppm).
(b) Actual reported value unclear but $\leq$ 0.02 ppm metsulfuron methyl as determined by fig. 3 of report.

As expected metsulfuron methyl is the major residue immediately after treatment. This residue decreases with time, and Metabolite A increases until four weeks after treatment, it is the major reported terminal residue. Minor metabolites reported are Metabolite Al, B, I, II, and saccharin. The low levels of total radioactivity at 0.22 ppm (of this 18.1% was identified) and 0.03 ppm as equivalent metsulfuron methyl in barley straw and grain, respectively, were not identified.

In the next field study, "Metabolism of [^{14}C] metsulfuron Methyl in Field Grown Wheat" authored by J. J. Anderson (Doc. No. AMR-199-84), 0.5 oz. a.i./A (0.035 lb/A or 16 g/A) of [^{14}C] metsulfuron methyl was surface applied to wheat in the tiller stage. The herbicide was sprayed in solution of water/methanol/surfactant (wk), 90/10/0.25 (v/v/v). Fresh foliage was sampled at 0,1,2, and 4 weeks; straw and grain were sampled at 9 weeks (maturity). The fresh foliar samples were lyophilized, ground-up in a Waring blender, and stored in plastic bags at -20°C for analysis. Grain and straw were separated and blended in a Waring blender. Radioactivity in plant tissue was quantitated using combustion analysis, in which the CO_2 was trapped using New England Nuclear's Oxisorb-CO_2 and Oxiprep-2 Scintillation Cocktail added for liquid scintillation counting (LSC).

Plant tissue was extracted using cold 80% actone/20% H_2O at 40°C. The solution was sonicated for 3 minutes and the extraction solvent was separated by vacuum filtration. The solid material ("straw") from the above sonication was extracted repeatedly for a total of three times. These extracts were combined. Aliquots were examined for radioactivity using LSC. The extracted straw matrix was then suspended in 0.01 M potassium phosphate buffer (pH7), stirred overnight at room temperature, the sample separated by filtration, and the readioactivity in the supernatant determined using LSC. Radioactivity in the plant matrix was quantitated by combustion and LSC as described above.

The acetone/water extracts above were concentrated by rotary evaporation at 45°C, diluted with distilled water, the pH adjusted to 3 with phosphoric acid and sequentially extracted 3 times each with methylene chloride and n-butanol. The three methylene chloride extracts were combined and the three n-butanol extracts were combined. The pH of the remaining aqueous phase was adjusted to pH 7 with 1.0 N NaOH. Each of the above extracts and the aqueous phase were evaporated to dryness using rotary evaporation at 45°C. The residues were then either dissolved in methylene chloride (methylene chloride extract) or in methanol (n-butanol extract and aqueous phase). Solubilized fractions were then analyzed using HPLC; the detector was not mentioned, but presumably, LSC and UV were used for labeled metabolites and standards, respectively. Unknowns were identified by comparison with standards synthesized by the petitioner.

Total radiolabel as equivalent metsulfuron methyl at various sample intervals were reported as:

Time (week)	ppm
0	1.87
1	0.76
2	1.08
4	0.12
9 mature straw	0.07
9 grain	<0.01

As illustrated in the above table, residues generally decrease with time after application. Within the limits of detectibility no radiolabel is reported in grain. The next table illustrates the reported percent extractability of radioactivity from the plant matrix samples using 80% acetone/20% water and phosphate buffer. Equivalent metsulfuron methyl in ppm is in parenthesis.

Time (week)	Acetone/Water	Phosphate Buffer	Unextracted
0	96 (1.79)	3 (0.06)	1 (0.02)
1	92 (0.70)	6 (0.05)	1 (0.01)
2	82 (0.88)	16 (0.18)	2 (0.02)
4	89 (0.11)	7 (0.01)	4 (<0.01)
9 straw	39 (0.02)	21 (0.02)	40 (0.03)

For all samples but straw, 82 to 96% of the radiolabel is solubilized by the acetone/water solution. Most of the remaining label is extracted using the phosphate buffer. Except for straw little if any radiolabel material remains unextractable in the sample matrix. However, for straw, 39 and 21% of the radionuclide is solubilized by the acetone/water and phosphate buffer solution, respectively. The amount of unextractable radiolabel was 40%. Because the amount of radionuclide, reported as equivalent metsulfuron methyl was <0.01 ppm the mature grain sample was not analyzed. The acetone/water fraction of all other samples were partitioned in methylene chloride and n-butanol; the radiolabel was identified as metsulfuron methyl, Metabolite A1 and Metabolite I in the methylene chloride fraction, with Metabolite A as the major metabolite reported in the n-butanol extract and metabolites, I, II, III and saccharin were noted in both the n-butanol and aqueous fractions. The radioactivity in the phosphate buffer was not identified due to interference of plant biomolecules.

Reporting as a percentage of total activity in fresh sample, metsulfuron methyl was the major residue at 75% for zero time; for samples at time 1 to 4 weeks, metsulfuron methyl was 7.4 to 17%, Metabolite A was 16.7 to 21%, Metabolite A1, 2.8 to 8.3%, Metabolite I, 8.3 to 17.1%, Metabolite II, 5.3 to 10.2%, Metabolite III, 0 to 8.3% and saccharin, 8.3 to 13%. Only a small amount of metabolite I (0.01 ppm) was reported in straw; the remaining activity (0.06 ppm) was not identified.

In the wheat and barley field metabolism studies (AMR-199-84 and AMR-211-84) 14% (0.12 ppm) to 25% (0.19 ppm) of the post plant applied radiolabeled residue was unidentified in the 1 week samples. This unidentified residue increased to 25% (0.32 ppm) to 39% (0.42 ppm) at 2 and 4 weeks post treatment. These studies were conducted at 4X the maximum proposed post plant application rate. The greenhouse study (AMR-106-83) conducted with wheat at 4 to 8X the requested maximum post plant application rate failed to identify 23 to 65% (0.29-1.36 ppm of equivalent metsulfuron methyl) of the 2 to 4 week samples. It is necessary to identify these unknown residues in forage. An alternative is discussed in the Residue Data section below; if the petitioner agrees to a 28 day grazing, and forage and hay harvesting restriction, and assuming no problems with the triazine plant metabolism study requested below, we could conclude the nature of the residue in plants is known for this proposed use.

No information on the fate of the triazine portion of the molecule has been submitted. The petitioner should submit a small grain plant metabolism study which depicts the fate of the triazine portion of the parent molecule. The ring carbon(s) of the triazine moiety should be radiolabeled.

Summarizing the metabolism of [^{14}C-phenyl] metsulfuron methyl reported, parent is catabolized to its major breakdown product, Metabolite A (glucose conjugate of Metabolite A1), and Metabolite A1, I, II, III and saccharin. RCB will reserve its recommendation for the tolerance expression until the fate of the triazine moiety is determined.

Animal Metabolism

Metabolism studies for metsulfuron methyl in rats and the goat were submitted. A metabolism study of Metabolite A in the goat, was also submitted.

In the study "Metabolism of ^{14}C-Metsulfuron Methyl in Rats" by Oliver R. Hunt (Document No. AMR-108-83), three groups of 4 Charles River CD® rats each (2 male and 2 female) were orally dosed with ^{14}C-phenyl labeled metsulfuron methyl. Group 1 was given a single dose of 16 mg labeled compound/kg; Group 2 was dosed with 16 mg/kg of labeled compound after preconditioning with metsulfuron methyl at 100 ppm in the diet; Group 3 was given a single dose with 3000 mg/kg of labeled material and no preconditioning.

The petitioner selected the low dose for its no-effect level and the high dose for its effect in the rats. Metsulfuron methyl was freshly prepared in a corn oil-acetone mixture (9:1, v/v) with a specific activity of 8.62 microcuries/mg. The isotope compound had a 98% radiochemical purity. Immediately after dosing, rats were placed in separate glass metabolism chambers.

In the low dose groups, urine and feces were collected at 6,24,48 and 72 hours; sacrifice occurred after 72 hours. In the high dosed group samples were taken at 6 hours after dosing, then every 24 hours until sacrifice at 96 hours. Respired ^{14}C gases were collected in 2N sodium hydroxide; gases untrapped by the base was passed through copper oxide at 700°C, and the resulting carbon dioxide collected in a second 2N sodium hydroxide trap. At sacrifice, blood, fat, tissue and organs were collected. For total radioactivity urine, blood, cage washings and gas trap solution (2N sodium hydroxide) were mixed with scintillation cocktail and counted using LSC; feces, organs, tissue samples, hide and carcass were lyophilized, combusted, the resulting products trapped in New England Nuclear's Oxisorb®-CO_2 adsober, scintillation fluid added and the solution counted for total radioactivity using LSC. Weighted samples of feces, organs and tissues were extracted twice with n-hexane, six times with a methylene chloride/methanol mixture (1:1, v/v) and 16 hours with methanol in a soxhlet extractor. Aliquots of the extracts were analyzed for radioactivity using LSC. After dilution with water and the pH adjusted to 4, urine was successively extracted with hexane and methylene chloride; the pH was lowered to about 1 with hydrochloric acid and extracted again with methylene chloride. Radioactivity for all fractions was determined using LSC. Metabolites in urine and feces were characterized using TLC and standards; tissue and organs were examined for the presence of metsulfuron methyl using liquid chromatogrpahy and comparing the elution interval with standard. Metabolites in urine were further examined using mass spectrometry.

Within 72 hours after dosing, 89.18 to 103.12% of the radiolabel excreted in the urine, feces and cage wash (<6.5%). Total organs and tissue samples contained a reported 0.27 to 1.73% of the total dose. There did not appear to be any difference in the metabolic profiles between the preconditioned and non-preconditioned lower dosed groups. One Group 1 rat had 6.8% of the dose in its hide and was presumed contaminated by urine and feces; this lead to a high average value for the group, so it is not included in the summarized total amount of radiolabel in organs and tissue. Total recovery of the dosed radioactivity was 91.6% to 103.9% for all groups.

Metsulfuron methyl was the major extractable ^{14}C-residue in urine (77.9-89.5%, As a percent of applied radioactivity) for all groups. Small amounts of saccharin (0.6-3.9%), Metabolite I (0.1-0.7%), Metabolite II (1.5-3.4%) and methyl 2-[[[(amino) carbonyl]amino]sulfonyl]benzoate (Metabolite III) (0.1-1.5%) were also identified in urine. As a percent of applied radioactivity rat feces contained metsulfuron methyl (1.8-4.2%), saccharin (0.1-0.8%), Metabolite I and III ($\leq$1.5%), and Metabolite II (0.3-3%). Organs and tissues were examined solely for the presence of metsulfuron methyl (0.1-0.4% of the applied radiolabel).

In the low dosed animals, both non-preconditioned and preconditioned, samples of blood, brain, fat, heart, kidneys, liver, lungs, muscles, spleen, skin, testes/ovaries, carcass (not defined by petitioner) contained <0.01 to 0.07 ppm metsulfuron methyl equivalent.

The G.I. tract contained 0.14-0.15 ppm equivalent parent compound, and the hide had reported 0.48 to 4.25 ppm equivalent metsulfuron methyl. The high dose reported in/on the hide reflects the assumed contaminated animal (hide had 6.77% of the dosed radioactivity). In the high dosed group (3g/kg b.w.) brain had <0.1 ppm parent equivalent, while blood, fat, heart, kidneys, liver, lungs, muscle, spleen and testes/ovaries had 0.1 to 2.6 ppm equivalent metsulfuron methyl. Skin, carcass and hide contained 7.2, 13.2 and 25 ppm equivalent metsulfuron methyl, respectively. Metsulfuron methyl was identified as a percent of applied radioactivity as follows:

Sample	% Metsulfuran methyl, per se
Hide - low dose (1)	36 - 62
- high dose	54 - 63
G.I. Tract - low dose	24 - 31
- high dose, female	54
Carcass (2) - low dose, female	59
- high dose, male	78
Liver - low dose	14
- high dose, female	44
Kidney - high dose, female	71

(1) Values are for both male and female rats unless otherwise noted.
(2) Composition not defined.

The rat study shows that metsulfuron methyl and its metabolites are rapidly excreted in the urine and feces. Up to ten fold more label was excreted in the urine. In addition to parent compound, the major excreted metabolites identified were saccharin, Metabolite I, II and III. The only radiolabel compound analyzed for and found in organs and tissues was metsulfuron methyl and consisted of 36 to 78% of the radiolabel. Less than half the radiolabel in liver was identified. No determination was reported on the fate of the triazine portion of the molecule. The term carcass was used in Tables IV, V, VI, XI, and XIV, should be defined. Skin and hide are also used; the petitioner should describe what they are calling skin and hide. Even ignoring the contaminated sample in Group I, radiolabel does appear to concentrate in the hide at the low dose and the skin and carcass at the high dose.

In the ruminant metabolism study "Metabolism of ^{14}C-Metsulfuron Methyl in the Goat" by C. Rapisarda (Doc. No. AMR-124-83, 5/29/84), a lactating goat (55 kg) was dosed by capsule with [^{14}C-phenyl (U)] metsulfuron methyl at 3.4 ppm in the diet (ca 5 mg (17.6 uCi) /dose) for five days. The specific activity of the sample dose was 3.5 uCi/mg milk, urine and feces were collected and combined daily. Sacrifice occurred 24 hours after the last dose, and rumen,

stomach and intestinal contents, hide, muscle, fat, blood and organs were collected for analysis. The material balance was reported as 96%. Aliquots of milk, urine and blood were mixed with scintillation cocktail and the radioactivity counted using LSC. Samples of tissues, organs, fat, feces, hide, rumen, stomach and intestinal contents were lyophilized and the radioactivity counted after combusting to $^{14}CO_2$, trapping in base, adding appropriate scintillation cocktail and using LSC.

Milk was defatted using n-hexane followed by a methanol extraction. The fat fraction containing a reported <1% of the radiolabel in milk, was discarded. The methanol/aqueous phase was extracted with chloroform; the aqueous and chloroform phases were each counted using LSC. The two fractions were then concentrated and analyzed using TLC, (dichloromethane/methanol/conc. ammonium hydroxide, 144/50/6,v/v/v) and the radioactivity located using autoradiograms. Radiochromatograms using a TLC radioscanner were also generated. The Rf values of the unknowns in the TLC plates were compared with standard compounds. Milk contained 0.009 ppm of equivalent ^{14}C-metsulfuron methyl. Intact ^{14}C-metsulfuron methyl was reported as accounting for 97% of the total radiolabel in the chloroform extracts and 78% of the combined aqueous and chloroform fractions. Methyl 2-[[[[(4-hydroxy-6-methyl-triazin-2-yl)amino]carbonyl]amino] sulfonyl]benzoate (Metabolite B, (not the same Metabolite B as reported in the above plant metabolism studies) was detected at 0.001 ppm (11% of the radionuclide in milk). Less then 0.001 ppm was reported for the metabolites (<11% of the label in milk), Metabolite I, II, saccharin, Metabolite B, 2-[[[[(4-methoxy-6-methyl-triazin-2-yl)amino]carbonyl] amino] sulfonyl] benzoic acid (Metabolite IV), and 2-[[[[(4-hydroxy-6-methyl-triazin-2-yl) amino]carbonyl]amino]sulfonyl]benzoic acid (Metabolite C). Polar materials remaining at the origin were also reported as <0.001 ppm.

As reported for rats, the majority of the radioactivity was excreted in the urine (60-100.7%). Approximately 8.4-35.2% of the dosed radioactivity was excreted in feces. In both urine and feces, metsulfuron methyl was the major metabolite (48.8-87%) reported. The remaining metabolites reported as 0.2% to 26.2% were the same as noted in the milk samples above.

Lyophilized liver, containing 3 ppb of equivalent metsulfuron methyl, was homogenized and extracted with n-hexane, to remove the fat, and chloroform. These fractions were reported as containing <1% ^{14}C and was discarded. The extracted liver was hydrolyzed with Pronase® in pH7, 0.01M K-PO_4 buffer, centrifuged, and the supernatant extracted with ethyl acetate. The aqueous phase contained <0.001 ppm or <5% extractable equivalent metsulfuron methyl. The ethyl acetate phase contained 45% or 1 ppb (equiv. metsulfuron methyl) of the extractable radiolabel. The solid liver material was further hydrolyzed with sodium hydroxide and extracted with acetonitrile. The aqueous-acetonitrile extract was partitioned with ethyl acetate. The aqueous phase, with <1% ^{14}C, was discarded, and the ethyl acetate fraction containing 50% or 1 ppb equivalent metsulfuron methyl, was concentrated and

analyzed using TLC. The major residues identified as % of total activity in liver (the parts per billion range in parenthesis) were metsulfuron methyl, 20% (<1) Metabolite I, 10% (<1), Metabolite II, 10% (<1) and saccharin, 55% (2).

Except for the observation of Metabolite V in urine, there was no discussion of the fate of the triazine portion of the parent molecule in animal tissue.

From the above discussion, it is apparent the major excretion pathway for the parent compound is through the urine. Lesser amounts are excreted in feces. Little radioactivity was reported in tissue and organs (1 ppb to 20 ppb). The major terminal residues in milk were metsulfuron methyl and methyl 2-[[[[(4-hydroxy-6-methyl-triazin-2-yl)amino]carbonyl]amino]sulfonyl] benzoate. The major residues reported in liver, the only tissue analyzed and radiolabeled compounds identified, were saccharin (probably in equilibrium with Metabolite II, and metsulfuron methyl. Metabolite I was also reported at approximately 10% of the radiolabel in liver.

In the final large animal metabolism study submitted ("Metabolism of the ^{14}C-Metsulfuron Methyl Wheat Metabolite A in a Goat", by O.R. Hunt and J.J. Anderson, Doc. No. AMR-156-83), a lactating goat was dosed on 5 consecutive days with 3.4 gram portions of wheat extract containing 38.7 mg of "^{14}C-wheat-metabolites" (spec. act. = 1.12 microCi/mg). The radiochemical purity as Metabolite A was reported as 45%. Each portion also contained 12% metsulfuron methyl, 11% Metabolite A1 (the exocon), and less than 1% Metabolite III. Milk was collected twice a day and the two milkings composited. Urine and feces were also collected daily. Twenty-one hours after the last dose, the goat was sacrificed and samples of blood, brain, heart, kidney, liver, pancreas, muscle (includes leg, flank and lion) and fat (back, omental, peripheral, and renal) were collected; the carcass was "sectioned". Radioactivity in liquid samples were quantitated using LSC; solid samples were combusted, the CO_2 trapped and the radioactivity quantitated using LSC.

After five days, 57% and 21% of the labeled compounds were excreted in the feces and urine, respectively. The animal's intestines contained 8% of the radiolabel. The major identified radiolabeled metabolites in feces and urine were metsulfuron methyl, Metabolite A, Metabolite A1 and Metabolite III. Radioactivity in all milk, and tissue/organ samples was reported as <0.015 ppm and <0.075 ppm, respectively.

No data was submitted on the fate of the triazine portion of the molecule.

The petitioner noted on p.3 of this report that the radiochemical purity of Metabolite A was 45% and included 12% metsulfuron methyl, 11% Metabolite A1 and less than 1% Metabolite III. No documentation was presented for this analysis. The petitioner should submit documentation for their analysis of the radiochemical

composition of the sample portions fed to the goat in this experiment. It was also reported that Metabolite A was fed at a rate equivalent to 38 ppm in the diet. The petitioner should explain how they calculated this value.

Assuming satisfactory answers to the above questions for this experiment, feeding of Metabolite A at 38 ppm in the diet for five days leads to non-detectable residues in milk (<0.015 ppm) and tissues (<0.075 ppm).

Saccharin is an approved "food additive permitted in food on an interim basis or in contact with food pending additional study" (see 21CFR 180.37), and, unless informed otherwise by TOX, is not a Residue Chemistry concern at this time.

From the above studies using [^{14}C-phenyl(U)] metsulfuron methyl the major terminal residues of concern in ruminants is the parent compound, metsulfuran methyl.

No poultry metabolism study was submitted. This study may be needed if future tolerance requests show significant residues in poultry feed items.

Analytical Method

No analytical method to determine metsulfuron methyl in small grain crops was submitted with this petition. However, a description of a method was submitted and reviewed in PP#3G2834 (J. Worthington, 4/13/83). As previously summarized, metsulfuron methyl is extracted from small grain samples with acetone:sodium acetate (80:20). The supernatant is collected after centrifugation and a 25 ml aliquot is diluted with a sodium bicarbonate buffer and washed with methylene chloride. The bottom methylene chloride phase was discarded, the pH of the aqueous phase adjusted to 3.5 with 10% hydrochloric acid and partitioned with toluene. Acetic acid was added to the toluene phase containing the metsulfuron methyl residue before concentrating to 1 ml and blown dry for storage in the freezer or HPLC analysis. Before analysis using HPLC, the dried sample is dissolved in 2 ml of the mobile phase and quantitated using a photo-conductivity detector equipped with a mercury lamp.

The detection limit (sensitivity) was reported as 0.02 ppm in barley, wheat, and soybean grain, rapeseed, corn, wheat and kidney bean green forage, and 0.05 ppm for wheat straw. Recovery values ranged from 60% to 110%. Specifically for wheat grain, recovery values ranged from 66% to 95% and averaged 82%.

No sample chromatograms were submitted for control and metsulfuron methyl fortified samples of barley grain, straw and green forage. These should be submitted for our review.

Assuming no problems are identified with the above requested sample chromatogram for barley grain, straw and green forage, the submitted methodology to determine metsulfuron methyl in barley

and wheat plant material appears adequate as an enforcement method. Our final endorsement of this method for enforcement purposes will follow a successful method-try-out. Before a method-try-out can be requested, the petitioner must submit clean copies of the methodology without the "Confidential" and "not for publication" labels.

Separate methodology has been proposed to determine methyl 2-[[[[(4-methoxy-6-methyltriazin-2-yl)amino]-carbonyl]amino]sulfonyl]-4-beta-D-glucopyranosylbenzoate (Metabolite A) in grain and green forage samples. A summary of this analytical method follows. A grain or green forage sample is homogenized in a mixture of acetone/sodium acetate buffer (80:20), centrifuged, and the supernatant decanted through glass wool. The extraction and centrifugation was repeated twice more with the acetone/sodium acetate buffer (80:20). After all extractants of each sample were combined, an aliquot was placed in a separatory funnel and the supernatant washed with a sodium citrate buffer, pH 6.5, and than methylene chloride to remove the acetone. Metabolite A in the aqueous phase was then subjected to enzymatic hydrolysis overnight (>16 hrs.) at pH 6.5 and 35°C using beta-glucosidase (from almonds, Type II, Sigma Chemical Co., St. Louis, Mo.)

After overnight hydrolysis, the pH of the reaction mixture was adjusted to 3.0, Metabolite A1 (exocon) extracted with chloroform and the mixture centrifuged. The chloroform phase was removed, taken to dryness, redissolved in chloroform and the residue cleaned-up using a silica Bond Elut® cartridge. Metabolite A1 was eluted from column using cyclohexane:2-propanol:methanol: glacial acetic acid:water (85:7.5:7.5:0.3:8). The eluted sample was concentrated to dryness redissolved in hexane:tetrahydrofuran: glacial acetic acid:water (70:30:2:5) and analyzed using HPLC and a UV detector at 254 mm.

Fortifications were performed using standard solutions of Metabolite A and samples were quantitated on the HPLC by comparing response factors derived using standard solutions of Metabolite A1. Chromatograms of untreated controls and fortified samples of wheat grain and wheat forage were submitted; the limits of detection for wheat grain and green forage are reported as 0.02 ppm and 0.05 ppm, respectively. No representative chromatograms for control and fortified barley grain straw and green forage were submitted. These chromatograms should be submitted for our perusal. The equation used to calculate the sample concentration contains the correction factor Pc, which in turn 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 requiring corrections due to interfering plant constituents. The petitioner should modify the proposed enforcement method for Metabolite A so a factor to correct for interference is not necessary.

It cannot be discerned from the given data whether free Metabolite A1 is determined with the conjugated Metabolite A1 in the analytical method for Metabolite A. The petitioner should verify that the enforcement method submitted for Metabolite A also determines any free Metabolite A1; otherwise the method should be modified so Metabolite A1 is determined. Validation data for Metabolite A1 should also be submitted.

All fortifications were performed with Metabolite A. Barley and wheat grain fortified at 0.02-0.16 ppm gave reported recoveries of 60-102%. Fortifying wheat forage at 0.05-0.40 ppm gave reported recoveries of 64-108%. The "Recovery Range" reported for barley forage fortified at 0.05-0.40 ppm was 0-90%. Yet the average recovery was noted as 80%. The petitioner should verify this "Recovery Range" of 0-90% is a typo and give the correct recovery range for these samples.

As discussed above, beta-glucosidase (Type II, from almonds) is used in the enzymatic hydrolysis step for the determination of Metabolite A as Metabolite A1. The petitioner should relate whether this is the only beta-glucosidase (Type II, from almonds) which will give satisfactory results in the hydrolysis step or will beta-glucosidases from other sources also give satisfactory results. Before we request a method-try-out for this analytical methodology using an enzymatic hydrolysis step, the petitioner should show that acid or base hydrolysis is not adequate.

Also, the enforcement analytical methodology proposed for both metsulfuron methyl and Metabolite A are marked confidential. We will need clean copies (not labeled confidential) of these methods before requesting a method-try-out.

The TLC systems described in the Nature of the Residue Section above will suffice for confirmatory methodology for parent and its catabolite Metabolite A.

Analytical methodology which determines metsulfuron methyl, per se in meat and milk is available in the study "Fate of Metsulfuron Methyl Ingested by Dairy Cows". Milk samples were extracted with water, 10% HCL and toluene mixture, centrifuged, and the toluene layer removed. The sample was extracted two more times with toluene, the toluene extracts combined and ran through a Bond Elut® cartridge and discarded. Metsulfuron methyl was eluted using the HPLC mobile phase and then the solvent was evaporated off under nitrogen. The residue was dissolve in solution A [cyclohexane:methanol:2-propanol (6:1.7:1)] and analyzed using HPLC and a photoconductivity detector.

Additional clean up of the milk fat sample was described. After elution from the silica Bond Elut® cartridge and evaporation to dryness, acetonitrile was added and partitioned three times with hexane. The residue in acetonitrile was evaporated to dryness, dissolved in solution A and analyzed as described for milk above.

After putting through a meat grinder, tissues were homogenized and extracted in a mixture of acetone and buffer B [water:sodium acetate:glacial acetic acid (2000:1.6:1)]. The sample was centrifuged and the supernatant decanted. After two more extractions with solution B, the extractant was partitioned in turn with a solution of sodium carbonate, methylene chloride, and toluene after acidification with hydrochloric acid. The toluene eluent was passed through a silica Bond Elut® cartridge and metsulfuron methyl eluted, dried down, resolubilized and analyzed as described for whole milk above.

Animal fat was freeze ground, homogenized with hexane and acetonitrile, the acetonitrile removed and the sample extracted twice more with acetonitrile:hexane (60:10). The acetonitrile extractants were combined and partitioned with buffer B. The remaining procedure was reported as for tissue above.

Milk, cream, skim milk, kidney, lean meat and liver were fortified at 0.01-0.02 ppm, 0.01-0.1 ppm, 0.025-0.5 ppm, 0.01-0.05 ppm, 0.01-0.05 ppm and 0.01-0.05 ppm, respectively, gave recoveries ranging from 69-118% and average recoveries ranged from 78-94%

with standard deviations of 5-11%. Fortification of subcutaneous fat at 0.01-0.05 ppm gave reported recoveries ranging from 54 to 85%, an average recovery of 73% and a standard deviation of 15%.

An enzymatic hydrolysis procedure for urine and milk is also described. Water is added to sample which was previously extracted for metsulfuron methyl, the pH adjusted to 5 with phosphoric acid and incubated for 20 hours at 35°C with beta-glucuronidase/sulfatase. After completion of the incubation period the solution is extracted four times with toluene and the toluene extracts passed through a silica Bond Elut® cartridge, metsulfuron methyl eluted with solution A and analyzed as previously described for milk above. The discussion indicates this assay determines conjugate(s) of metsulfuron methyl as metsulfuron methyl. Because it is not expected that beta-glucuronidase or sulfatase enzymes would release exocons as metsulfuron methyl, the petitioner should explain why their discussion indicates it would.

Analytical methodology may be needed for poultry tissue and eggs for any future use where significant poultry feed items are involved.

If significant metabolites containing the triazine moiety are reported in the plant metabolite studies requested above, additional analytical methodology adequate for enforcement purposes may be needed.

Residue Data

Residue data on wheat, and barley grain and straw were submitted for parent and Metabolite A from the major barley and wheat growing areas of California, Colorado, Delaware, Idaho, Illinois, Kansas, North Dakota, Montana, Ohio, Oklahoma, Oregon, South Dakota and Washington State. Most data represented ground application in 12 to 40 GPA; aerial application consisted of 1-7 GPA. Residue data in wheat green forage was submitted from Kansas, North Dakota, Oklahoma, and Oregon; residue data for barley green forage was submitted from California only. One application of 0.06-1.0 oz. a.i./A (X-16X) gave reported residue of <0.02 ppm for parent and Metabolite A in/on wheat and barley grain, and <0.05 ppm in/on wheat and barley straw for PHI ranges of either 21-135 days or 220-327 days. Using one application of 0.125 oz. a.i./A on wheat green forage lead to reported residues for parent of 0.08 ppm to 0.76 ppm, <0.05 ppm to 0.11 ppm and <0.05 ppm at 0-1 day PHI, 3-7 days PHI and 14-28 days PHI, respectively. One application of 0.25 oz. a.i./A on wheat green forage gave reported residues for parent of <0.05 ppm to 2.2 ppm, <0.05 ppm to 0.21 ppm and <0.05 ppm at 0-1 day PHI, 3-7 days PHI and 14-28 days PHI, respectively.

Residues of Metabolite A in wheat green forage treated at 0.125-0.25 oz. a.i./A (X-2X) were reported as 0.06 ppm to 0.7 ppm at 0 day PHI, <0.05 ppm-0.08 ppm at 1-3 days PHI and <0.05 ppm at 7-28 days PHI. Applications of 0.06-0.50 oz. a.i./A (1X-8X) to barley green forage lead to <0.05 ppm for both parent and Metabolite A (0.06-0.25 oz. a.i./A only) for 37-74 days PHI. Field trials results submitted in PP#3G2834 (J. Worthington, 3/16/84) gave parent residues within the ranges and application rates reported here.

Several different surfactants and concentrations were used in the above residue trials. No relationship between brand or concentration of surfactant and residue level is evident under these experimental conditions.

No storage stability studies or raw residue data were submitted in this submission. The petitioner was informed in our review of April 13, 1983 (J. Worthington, PP#3G2834) for future permanent tolerance requests, storage stability data would be needed demonstrating that residues are stable under the conditions of storage and raw data (including chromatograms) developed in the studies should be submitted. We continue to request storage stability data and raw residue data for both metsulfuron methyl and Metabolite A1. The raw residue data should include how the field samples were collected, stored before shipping, conditions of shipping and handling, and storage before analysis.

No residue data was submitted for hay. The petitioner could submit residue data on hay at the maximum proposed use or accept a restriction against harvesting treated barley and wheat for hay. Alternatively, a calculated exposure for the tolerance using

the succulent forage to day dry-down factor of 4 could be used. As noted in the Nature of the Plant Metabolism section above, identification of the unknown forage residues is needed. As an alternative, based on the results of the residue data and assuming no problems with the requested storage stability and triazine metabolism studies, we could conclude the nature of the residue in plants is understood for this proposed use, if the petitioner submits a revised Section B which includes a restriction against grazing or harvesting forage or hay until 28 days after treatment.

The tolerance expression will be in terms of at least metsulfuron methyl and its metabolite, Metabolite A1 (includes the exocon in Metabolite A) expressed as parent. However, we withhold our final conclusions on the adequacy of the requested tolerances and whether wheat and barley milling studies are needed until a revised Section B including a 28 day grazing and harvesting restriction, and the above requested data on the fate of the triazine moiety in plants has been submitted and reviewed, and the storage stability question noted above is satisfactorily resolved.

Meat, Milk, Poultry and Eggs

A cow feeding study was submitted to assess the fate of metsulfuron methyl in ruminants. Eight Guernseys were fed diets for four weeks containing 0,5,20 or 100 ppm metsulfuron methyl. Milk was collected twice daily and the AM and PM samples were composited at a ratio of 2:1 (AM:PM) to approximate the ratio of AM to PM milk production. Twelve hours after the last dose one animal from each dose group was sacrificed at the end of the 28 day experiment and tissues were collected. The second cow of each dose group was fed an unfortified diet for an additional 7 days and then sacrificed. Urine and feces were collected twice a week during the pre-treatment and treatment period, and daily during the post-treatment period.

Samples of metsulfuron methyl treated feed (mash) were stored frozen after mixing. Fortified mash was analyzed weekly. The calculated concentration was 4840 ppm. Analyzed concentrations were reported as 4850, 3980, 4550 and 3520 ppm at 0 (presumably), 2, 3 and 4 weeks after batch mixture of treated feed was prepared. No validated methodology or sample chromatograms for the fortified mash analysis were submitted. These should be submitted.

Analysis of milk samples show that residues of metsulfuron methyl, per se, plateau 2 to 4 days after start of the 20 ppm and 100 ppm treatment levels. At the 5 ppm feeding level, milk from one cow had no reported residues (<0.01 ppm); three composited milk samples from the other cow showed only trace amounts of residue (0.01 ppm-0.011 ppm), and no residues (<0.01 ppm) in the remaining samples. Separate analysis of skim milk and cream from two separate milkings indicate no concentration of metsulfuron methyl in either fraction.

Analysis of fat and muscle gave reported values of <0.01 ppm for both commodities at all feeding levels and both groups of animals. Metsulfuron methyl residues in kidney were reported as 0.05 ppm, 0.82 ppm and 0.12 ppm at the 5,20, and 100 ppm feeding levels for all animals slaughtered at the end of the treatment period and <0.01 ppm at all feeding levels for those animals slaughtered 7 days post-treatment. The petitioner claims ^{14}C-urine contamination of the kidney from the intermediate feeding level. All controls were <0.01 ppm.

In the text of the study, analysis of liver samples were reported and a sample chromatogram for this tissue was submitted. However, the actual residue values for the three feeding levels were not included in Table 10. The petitioner should submit this missing data. Also, figure 9 relates to kidney samples of cow #7 containing 0.67 ppm metsulfuron methyl, yet this value is reported as 0.12 ppm in Table 10. The petitioner should explain this discrepancy.

The results of the analysis for urine and feces show most of the residues are excreted in the urine with a small amount excreted in the feces. These results are consistent with the animal metabolism studies discussed above.

No poultry feeding study was submitted. Both a poultry metabolism study (see above in Nature of the Residue section) and a feeding study may be needed if future tolerance requests show significant residues in poultry feed items.

This is category 2 of Section 180.1(a) with respect to secondary residues in meat and milk.

Livestock feed items in this petition are wheat and barley grain, straw, hay and green forage. the maximum calculated exposure to livestock (dairy cow) from eating treated feed items is:

Commodity	% in diet	Tolerance, ppm	Exposure, ppm
forage	40	5	2
hay (calculated)	60	20	12
		Total =	14 ppm

The maximum calculated exposure to livestock assuming the petitioner will accept a hay harvesting restriction is:

Commodity	% in diet	Tolerance, ppm	Exposure, ppm
grain	20	0.05	0.0
straw	10	0.02	0.0
forage	70	5.0	3.5
		Total =	3.5 ppm

Depending on the results of the liver data, and the triazine moiety question in plants, the petitioner should request a hay harvest restriction for this use; alternatively, the petitioner can submit residue data on hay treated at the maximum proposed rate and a minimum PHI and propose a tolerance. If the proposed tolerance (either supported by residue data or calculated) in hay causes the animal feed exposure calculated above to exceed 3.5 ppm, another goat ^{14}C-metabolism study should be submitted at higher feed levels, and tissue residue identified.

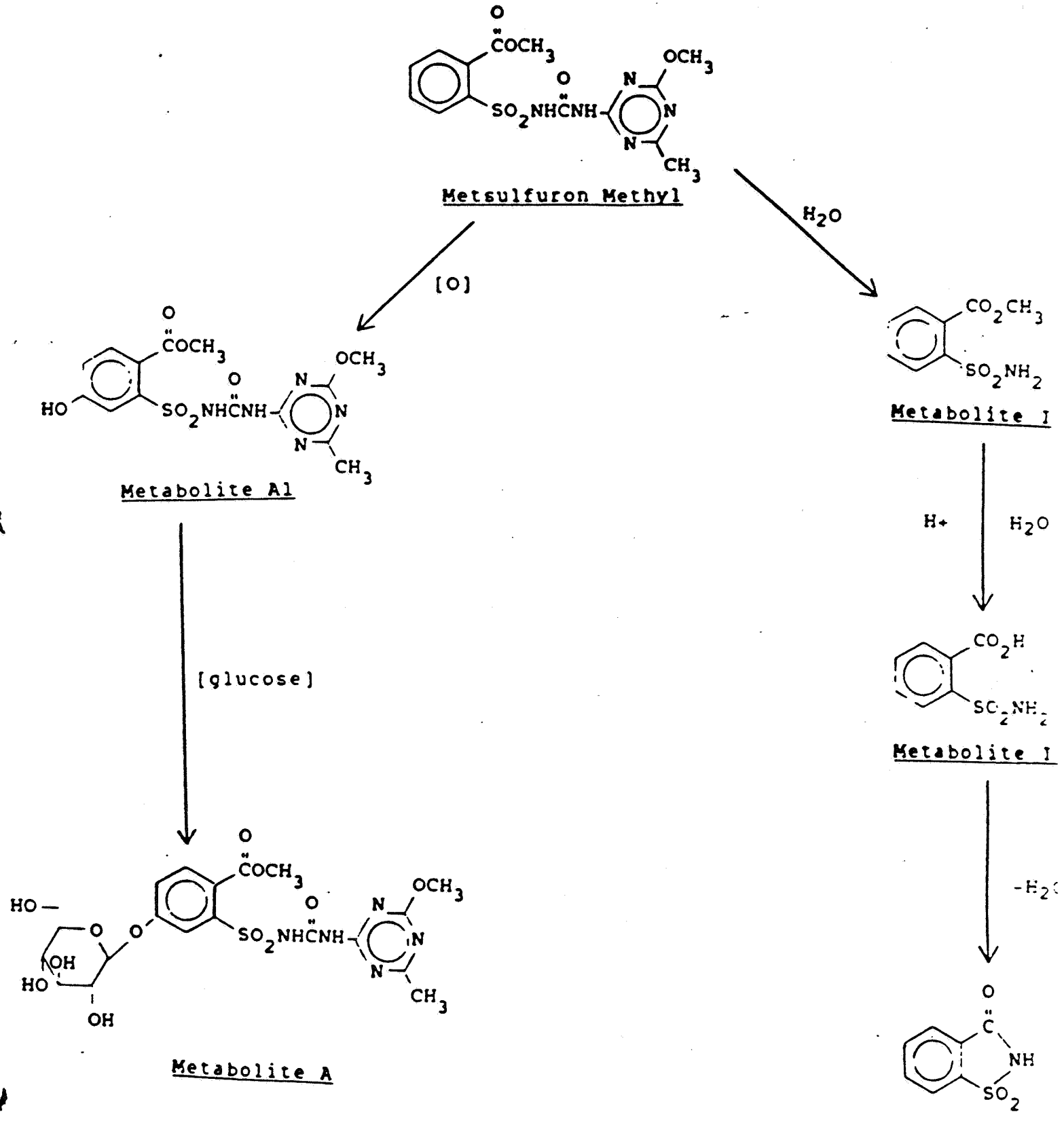
A restriction against harvesting small grains as hay and assuming satisfactory answers to the above kidney and liver data results and the triazine moiety question in plants, for this use, we can conclude the residue of concern in meat and milk is the parent compound, metsulfuron methyl, and we can tentatively recommend for the requested tolerances of 0.05 ppm in milk, and 0.1 ppm in meat (except kidney and liver), fat and meat byproducts. We withhold our recommendations on tolerances for kidney and liver until we have received and reviewed the requested liver residue data and kidney data information requested above.

If new metabolites of toxicological concern are found in the requested plant metabolism studies, additional animal feeding studies may also be needed.

cc:w/CBI:R.F., Reviewer, TOX, PP#4F3127, PMSD/ISB
cc:w/o CBI/Circu, EAB, EEB, FDA, Robert Thompson
RDI:PErrico:4/3/85
TS-769:CM#2:RM810:X7377:PErrico:wh:4/10/85

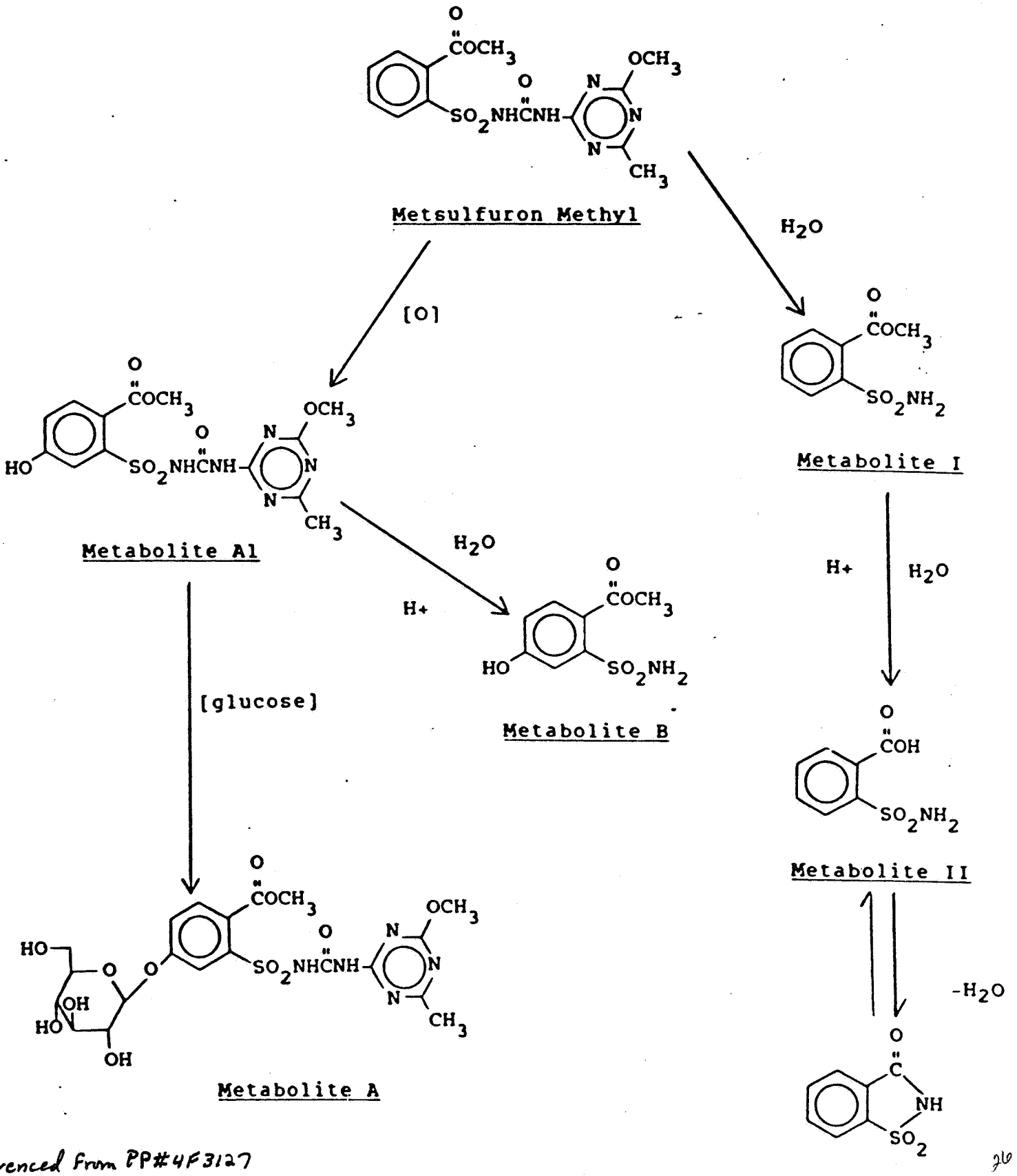
Attachments

SUGGESTED METABOLIC PATHWAY FOR METSULFURON METHYL IN WHEAT*



*Referenced from PP# 4F3127

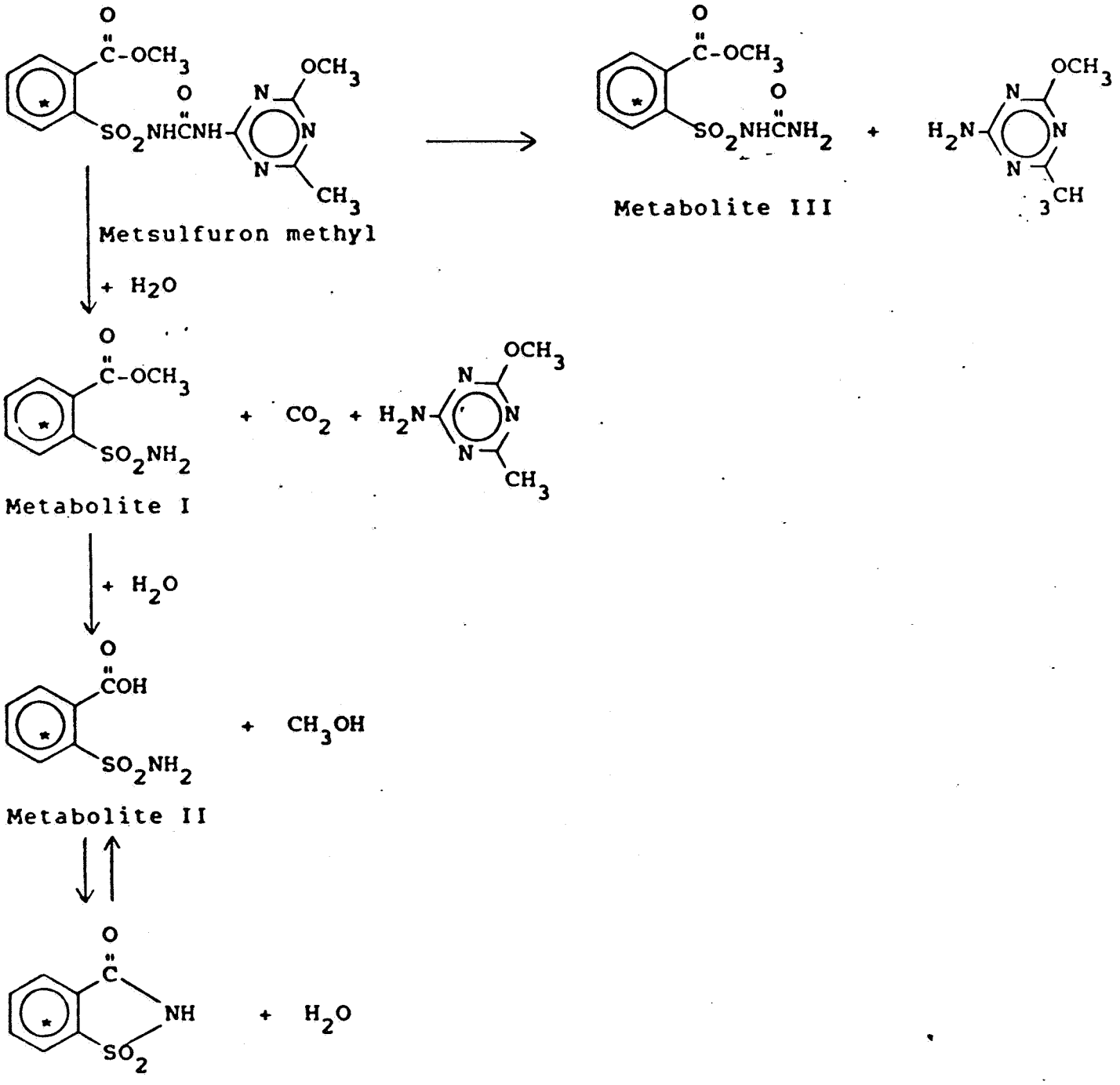
SUGGESTED METABOLIC PATHWAY FOR [^{14}C]METSULFURON METHYL IN BARLEY*



* Referenced from PP#4F3127

Metabolism of Metsulfuron Methyl*

These data suggest the following routes of metabolism in rats:



* Referenced from PP#4F3127

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL: metsulfuron methyl

PETITION NO. 4F3127

CCPR NO. _____

Reviewer: PVL
J. Lowe 12/6/84

Codex Status

Proposed U.S. Tolerances

[/] No Codex Proposal Step 6 or above

Residue (if Step 9): _____

Residue: Parent + at least methyl 2-[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-4-β-D-glycopyranosylbenzoate

Crop(s) Limit (mg/kg)

Crop(s) Tol. (ppm)

CANADIAN LIMIT

Residue: _____

Crop Limit (ppm)

none

MEXICAN TOLERANCIA

Residue: _____

Crop Tolerancia (ppm

none

NOTES:

Page 29 contains the manufacturing process for the product. This page is not included.