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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

**MEMORANDUM**

DATE: 12/17/01

SUBJECT: PP#3F4215. Request for the Use of Metsulfuron Methyl on Grain Sorghum. Evaluation of Analytical Chemistry and Residue Data including Poultry Metabolism Study.

DP Barcode: D232665
Submission #: S517121
Chemical#: 122010
Trade Name: ALLY® HERBICIDE
EPA Reg#: 352-435
MRID#: 44155601, 44179301, 44477801

PRAT Case#: 284688
Caswell#: 418H
Class: Herbicide
40 CFR: 180.428

FROM: William D. Cutchin, Chemist
SIMB/HED (7509C)

THRU: Richard A. Loranger, Branch Senior Scientist
RAB2/HED (7509C)

TO: Jim Tompkins/Vickie Walters, PM Team 25
Fungicide-Herbicide Branch
Registration Division (7505C)

Following is the chemistry assessment of a petition from E.I. du Pont de Nemours and Company, Inc. proposing permanent tolerances for residues of metsulfuron methyl {methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]-amino]sulfonyl]benzoate}. The petitioner is proposing the establishment of tolerances for residues of metsulfuron methyl in/on: sorghum, grain at 0.1 ppm, sorghum, forage and stover at 0.2 ppm. The review was performed by the Dynamac Corp. under the supervision of SIMB and RAB2, HED. The data assessment has undergone secondary review within the branch and has been revised to reflect current HED and OPP policy. If any additional input is needed, please advise.

**Executive Summary of Residue Chemistry Deficiencies**

- Revised Section F specifying the tolerance expression for metsulfuron methyl and its metabolite as stated in 40 CFR: 180.428(a).

# Metsulfuron-methyl

## PC Code 122010
## (DP Barcode D232665)

## Permanent Tolerance Petition (PP#3F4215) for Use On Grain Sorghum

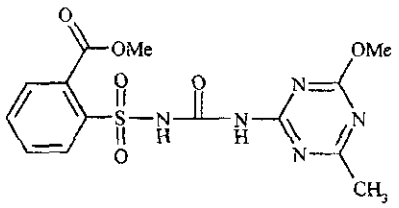
November 12, 1999

Contract No. 68-W99-053

Submitted to:
U.S. Environmental Protection Agency
Arlington, VA

Submitted by:
Dynamac Corporation
1910 Sedwick Road
Building 100, Suite B
Durham, NC 27713

# METSULFURON-METHYL



PERMANENT TOLERANCE PETITION (PP#3F4215)

FOR USE ON GRAIN SORGHUM

PC Code 122010

(DP BARCODE D232665)

## INTRODUCTION

E.I. du Pont de Nemours and Company, Inc. has proposed the following permanent tolerances for residues of metsulfuron methyl {methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]-amino]sulfonyl]benzoate} in/on:

| | |
|---|---|
| Sorghum, grain | 0.1 ppm |
| Sorghum, forage | 0.2 ppm |
| Sorghum, stover | 0.2 ppm |

In conjunction with the above tolerance proposals, the petitioner is applying for a Section 3 registration of Ally™ Herbicide (EPA Reg No. 352-435), a 60% dry flowable (DF) formulation of metsulfuron methyl, for postemergence control of broadleaf weeds and some annual grass weeds in grain sorghum. This tolerance proposal, together with associated residue chemistry data, has been previously reviewed by the Agency (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94 and DP Barcodes D211879 & D211881, M Flood, 4/4/95). In response to deficiencies cited in these reviews, the petitioner has submitted additional residue chemistry data.

Tolerances for the combined residues of metsulfuron methyl and its metabolite methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-4-hydroxybenzoate [A1] are established under 40 CFR 180.428(a) in/on the following raw agricultural commodities (RACs): barley/wheat grain (0.1 ppm), hay (20.0 ppm), and straw (0.3 ppm); wheat green forage (5.0 ppm); grass forage, fodder, and hay (15.0 ppm each); and sugarcane (0.05 ppm). Tolerances for residues of metsulfuron methyl *per se* are established under §180.428(b) in fat, meat, and meat byproducts of cattle, goats, hogs, horses and sheep at 0.1 ppm; in kidney of cattle, goats,

hogs, horses and sheep at 0.5 ppm; and in milk at 0.05 ppm. There are currently no tolerances for residues of metsulfuron methyl in food/feed processed commodities.

Three volumes of residue chemistry data associated with this petition are evaluated in this document.

CONCLUSIONS

OPPTS 830 Series GLNs: Product Properties

1. HED has previously determined that there is adequate product chemistry data for the technical product containing the active ingredient metsulfuron methyl. No impurities are expected to cause residue concerns.

OPPTS GLN 860.1200: Proposed Uses

2. The proposed use directions for use on grain sorghum have been previously reviewed and considered adequate. The proposed use directions allow a single application of metsulfuron methyl to grain sorghum prior to boot stage at 0.0019 lb ai/A/season.

OPPTS GLN 860.1300: Nature of the Residue - Plants

3. The nature of the residue in cereal grains is adequately understood based on acceptable metabolism studies on wheat and barley (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94). The residues of concern are metsulfuron methyl *per se*, and its metabolites, methyl 2-[[[[(4-methyoxy-6-methyltriazin-2-yl)amino]carbonyl]amino] sulfonyl]-4-beta-D-glycopyranosyl- benzoate (Metabolite A) and methyl 2-[[[[(4-methoxy-6-methyltriazin-2-yl)amino]carbonyl]amino]sulfonyl]-4-hydroxybenzoate (Metabolite A1). The chemical names and structures of metsulfuron methyl and its metabolites in plants are shown in Attachment 1 (Figure A).

OPPTS GLN 860.1300: Nature of the Residue - Ruminant

4a. The Agency has previously concluded that the nature of the residue in ruminants is adequately understood for the purposes of the petition on grain sorghum. The residue of concern is metsulfuron methyl *per se* (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94).

OPPTS GLN 860.1300: Nature of the Residue - Poultry

4b. The nature of metsulfuron methyl residues in poultry is adequately understood. Two groups of five hens were dosed over 5 consecutive days with [phenyl-UL-$^{14}$C] or [triazine-2-

$^{14}$C]metsulfuron methyl at 12 ppm in the diet, equivalent to ~120x the maximum theoretical dietary burden for poultry resulting from proposed or registered uses.

4c. The total recovery of dosed radioactivity was 103.0 and 105.7% for [phenyl-$^{14}$C] or [triazine-2-$^{14}$C]metsulfuron methyl, respectively, of which 102.9 and 105.3% of the administered dose was excreted. Radioactivity in egg and tissues (each <0.05-0.1%) together accounted for ≤0.2% of dosed radioactivity. Parent compound and its minor metabolite *O*-desmethyl metsulfuron methyl were identified as comprising 88-91% and 2-4% of the TRR in excreta (both labels), respectively.

4d. With the exception of [phenyl-$^{14}$C]-labeled egg whites, in which residues peaked on Day-2 at 0.047 ppm, possibly due to contamination by a small amount of excreta, $^{14}$C-residues in eggs increased throughout the dosing period, reaching maximum levels on Day-5 at 0.005-0.021 ppm in yolks, and 0.037 ppm in [triazine-2-$^{14}$C]-labeled egg whites. The concentrations of $^{14}$C-residues in [phenyl-$^{14}$C]-labeled tissues were lower (<0.01 ppm except liver at 0.013 ppm) than those found in [triazine-2-$^{14}$C]-labeled tissues, suggesting that cleavage of the parent molecule may occur during metabolism. $^{14}$C-Residues in [triazine-2-$^{14}$C]-labeled tissues were highest in skin (0.036 ppm), followed by liver and muscle (0.021-0.025 ppm), and lowest in fat (0.003 ppm).

4e. Overall, >86% of the TRR in tissues and eggs was adequately identified or characterized. Solvent extraction released 75-94% of the TRR from tissues and egg, except for [phenyl-$^{14}$C]-labeled liver, from which 47.4% of the TRR was extracted. After partitioning with organic solvent(s), most of radioactivity remained in the aqueous fractions, which were subsequently analyzed by HPLC provided they contained $^{14}$C-activity >0.01ppm. $^{14}$C-Residues in organosoluble/unextracted fractions (≤0.004 ppm) were not further analyzed. Parent metsulfuron methyl was the principle component of the residue in [triazine-2-$^{14}$C]-labeled tissues, accounting for 8.6% of the TRR (0.001 ppm) in liver, 57.2% of the TRR (0.013 ppm) in skin, and 14.2% of the TRR (0.004 ppm) in egg white. A high level of parent was detected in [phenyl-$^{14}$C]-labeled egg white (88.0%TRR, 0.034 ppm); however, contamination of the sample with excreta is suspected. In addition to parent, the aqueous fraction of [triazine-2-$^{14}$C] labeled liver, muscle, skin, and egg white contained multiple polar to moderately polar components which eluted as broad regions of radioactivity each accounting for 35-85% of the TRR (≤0.022 ppm).

4f. Although a poultry feeding study and tolerances are not needed at this time, RAB2 will request that the Metabolism Assessment Review Committee (MARC) determine the residue of concern for possible future uses.

OPPTS GLN 860.1340: Analytical Methods

5a. The HPLC/UV method (Morse Laboratories SOP # METH-82, Revision No. 2) used to determine residues of metsulfuron methyl in/on grain sorghum RACs is adequate for data collection purposes. Adequate method validation data were submitted. The validated limit of

quantitation (LOQ) for residues of metsulfuron methyl *per se* is 0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage. The LOQ for the combined residues of Metabolite A1 (4-OH-metsulfuron methyl) and Metabolite A (metsulfuron methyl glucose conjugate), determined as Metabolite A1, is 0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage.

5b. The Agency has previously concluded that adequate methods are available for enforcement of tolerances for residues of metsulfuron methyl in/on plant and animal commodities. PAM Vol. II lists Methods I and III which are respectively capable of determining residues of metsulfuron methyl *per se* and the combined residues Metabolites A and A1 in/on wheat RACs. Method II determines metsulfuron methyl in ruminant tissues and milk.

OPPTS GLN 860.1360: Multiresidue Method

6. Metsulfuron methyl is not recovered by FDA Multiresidue Protocols.

OPPTS GLN 860.1380: Storage Stability Data

7a. The submitted storage stability data are adequate and indicate that residues of metsulfuron methyl and its metabolites, A1 and A, are stable in sorghum grain, forage, and stover for up to 9 months at -20±5°C. In addition, metsulfuron methyl and Metabolite A1 are stable in refrigerated (1-8°C) extracts of sorghum forage, grain, and stover for up to 8 weeks.

7b. These data resolve the deficiencies cited (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94) concerning the lack of storage stability data for residues of methyl metsulfuron in extracts stored under refrigerated conditions for extended periods (up to 6 weeks) prior to analysis. The data also support storage intervals incurred by the residue samples (up to 7.5 months) from each of the sorghum field trials performed in conjunction with the subject petition.

OPPTS GLN 860.1480: Meat/Milk/Poultry/Eggs

8a. The Agency has previously concluded that existing tolerances for residues in meat and milk will not be exceeded by the proposed use on sorghum grain. The proposed use on sorghum does not increase the maximum theoretical dietary burden of metsulfuron methyl residues for ruminants.

8b. For purposes of this petition, poultry feeding studies are not required. Based on results from the hen metabolism study and the maximum theoretical dietary exposure for poultry (0.1 ppm) resulting from the proposed uses on grain sorghum, there is no reasonable expectation of finite metsulfuron methyl residues being transferred to poultry tissues and egg. Therefore, tolerances for residues in poultry are not required at this time.

OPPTS GLN 860.1500: Crop Field Trials

9a. The Agency has previously reviewed data (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94) from six field trials on grain sorghum conducted prior to 1992 in CA, KS, MO, NC, OK, and TX. Residues of metsulfuron methyl *per se* and the combined residues of its two metabolites were each below the respective LOQ (<0.05 ppm for grain; <0.1 for forage and stover) in/on all treated samples of forage or mature grain and stover harvested ~30 or 66-97 days after application of metsulfuron methyl (60% DF) at 0.03-0.06 oz ai/A/season (1 or 2x). The Agency subsequently concluded (PP#3F4215, DP Barcode 211879, M. Flood, 4/4/95) that the proposed regional registration for use on sorghum might be obtained provided that the petitioner conduct two additional field trials in Region 8.

9b. The currently submitted residue data from two field trials (four tests) on grain sorghum are adequate. Residues of metsulfuron methyl *per se* and its metabolites A1 and A (determined as Metabolite A1) were not quantifiable (<0.1 ppm for grain and stover; <0.05 ppm for forage) in/on eight treated samples each of forage or mature grain and stover harvested 31-39 or 66-88 days, respectively, after treatment with metsulfuron methyl at 0.03 or 0.06 oz ai/A/season (1 or 2x).

9c. The geographic representation of the data and the number of tests conducted are sufficient to support the proposed regional registration of metsulfuron methyl for use on grain sorghum. The petitioner has conducted a total of four trials at 1-2x the proposed maximum rate and minimum PHI on grain sorghum in Region 8. The submitted data are adequate to support the proposed tolerances with regional registration for residues of metsulfuron methyl in/on sorghum grain at 0.1 and sorghum forage and stover at 0.2 ppm. However, a revised Section F should be submitted to include both the parent and metabolite in the tolerance expression as stated in 40 CFR: 180.428(a).

OPPTS GLN 860:1520: Processed Food/Feed

10. Based on a sorghum processing study, the Agency has previously concluded that metsulfuron methyl and its metabolites do not concentrate in grain sorghum processed commodities or aspirated grain fractions; therefore, no tolerances are required for residues in sorghum processed commodities.

OPPTS GLN 860.1850 and 860.1900: Confined/Field Accumulation in Rotational Crops

11. Previous recommendations restricted rotational crop intervals for up to 22 months. HED's policy no longer considers rotational crop intervals of greater than 12 months practical unless driven by phytotoxicity concerns. Therefore, the label can be amended to allow replanting of crops for which there are registered uses at any interval and for all other crops after 12 months unless the registrant wishes to retain the longer replant intervals due to phytotoxicity concerns.

Other Considerations:

There are no Mexican, Canadian or Codex MRLs established for metsulfuron methyl on grain sorghum. Therefore there are no compatibility issues to be reconciled.

## RECOMMENDATIONS

With the exception of the need for a revised Section F (Conclusion 9c), the submission of the current data fulfills the residue chemistry data requirements for the proposed use of metsulfuron methyl on grain sorghum (PP#3F4215). Pending the results of the forthcoming human health risk assessment, RAB2 recommends for metsulfuron methyl tolerances with regional registration in/on: sorghum, grain at 0.1 ppm, sorghum, forage and stover at 0.2 ppm.

## DETAILED CONSIDERATIONS

### OPPTS 830 Series GLNs: Product Properties

The manufacturing process was summarized in J. Worthington's 7/1/86 memo for PP#6G3398. No problems with impurities were anticipated. HED has previously concluded (PP#3F4215, DP Barcode D191296, M. Flood, 6/7/94) that adequate data are available to fulfill product chemistry data requirements.

### OPPTS GLN 860.1200: Proposed Uses

The proposed use directions for the 60% dry flowable (DF) formulation of metsulfuron methyl (product name = ALLY® HERBICIDE; EPA Reg. No. 352-435) on grain sorghum have been previously reviewed and considered adequate. The proposed use directions allow a single application of metsulfuron methyl to irrigated or dryland grain sorghum prior to the boot stage at 0.03 oz ai/A/season (0.0019 lb ai/A), and restricts use to CO, KS, NE, NM, OK and TX. (Refer to PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94 and DP Barcodes 211879 & 211881, M Flood, 4/4/95 for a summary of the proposed use pattern).

### OPPTS GLN 860.1300: Nature of the Residue - Plants

The nature of the residue in cereal grains is adequately understood based on acceptable metabolism studies on wheat and barley; no additional plant metabolism data are required to support the petition for use on grain sorghum (DP Barcodes D191296 & D191298, M. Flood, 6/7/94). The residues of concern are metsulfuron methyl *per se*, and its metabolites, methyl 2-[[[[(4-methyoxy-6-methyltriazin-2-yl)amino]carbonyl]amino]sulfonyl]-4-beta-D-glycopyranosylbenzoate (metabolite A) and methyl 2-[[[[(4-methoxy-6-methyltriazin-2-yl)amino]carbonyl]amino]sulfonyl]-4-hydroxybenzoate (metabolite A1). The chemical names and structures of metsulfuron methyl and its metabolites are shown in Attachment 1 (Figure A).

## OPPTS GLN 860.1300: Nature of the Residue - Livestock

### Ruminants

The Agency has previously concluded (DP Barcodes D191296 & D191298, M. Flood, 6/7/94) that, for the purposes of the petition on grain sorghum only, the nature of the residue in ruminants is adequately understood; the residue of concern in ruminant commodities is metsulfuron methyl *per se*.

### Poultry

The Agency previously concluded that a poultry metabolism study should be submitted to support the proposed permanent tolerance petition for use of metsulfuron methyl on grain sorghum (DP Barcodes D191296 & D191298, M. Flood, 6/7/94). In response, the petitioner has submitted data (citation shown below) depicting the metabolism of [phenyl-UL-$^{14}$C] and [triazine-2-$^{14}$C] metsulfuron methyl by hens following multiple oral doses. The in-life phase of the study and determination of total radioactive residues in tissues, egg, and excreta were conducted by Battelle, Columbus, OH. The analytical phase was conducted by Dupont, Wilmington, DE.

> 44179301 Charlton, R.; Bookhart, S. (1996) Metabolism of (carbon-14) Metsulfuron Methyl in Laying Hens: Lab Project Number: AMR3554-95: N001761A. Unpublished study prepared by Dupont Agricultural Products and Battelle. 194 p.

The test substance uniformly labeled on the phenyl ring had a specific activity of 38.3 μCi/mg and a radiochemical purity of 99%. The test substance labeled at position 2 on the triazine ring had specific activity of 49.9 μCi/mg and a radiochemical purity of 99.0%. For dosing, both $^{14}$C-labels were diluted with non-radiolabeled metsulfuron methyl to final specific activities of 45,066 dpm/μg (phenyl-$^{14}$C) and 44,844 dpm/μg (triazine-2-$^{14}$C).

Two groups of five hens were dosed orally once daily with [phenyl-$^{14}$C] or [triazine-2-$^{14}$C] metsulfuron methyl for five consecutive days via capsule at a mean dose of 1.40 mg/hen/day. Based on average feed consumption for the dosing period, this dose level was equivalent to 12.1 and 11.8 ppm of metsulfuron methyl in the diet for [phenyl-$^{14}$C] and [triazine-2-$^{14}$C]-treated hens, respectively, equivalent to ~120x the maximum theoretical dietary exposure of 0.1 ppm for poultry. Additionally, two groups of three hens each were dosed with [phenyl-$^{14}$C] or [triazine-2-$^{14}$C]metsulfuron methyl, in the same manner as above, at dose levels equivalent to 121 and 72 ppm of metsulfuron methyl in the diet; samples from the high-dose groups were not analyzed, but were stored for possible use in metabolite characterization/identification.

Eggs were collected twice daily. Eggs collected in the afternoon following dosing were refrigerated overnight and composited, after separation into whites and yolks, with eggs collected the following morning prior to dosing. Excreta were collected daily prior to the initial dosing.

and at ~24 hour intervals thereafter. The animals were sacrificed 22-23 hours after the last dose, and muscle (breast and thigh and), fat, skin, liver, gizzard, blood, and the GI tract were collected. Samples were composited by dose groups and stored at ~-20°C until analysis.

Total radioactive residues (TRR)

Homogenzied samples of tissue, eggs, and excreta were solubilized (by incubation at 50°C) and radioassayed in triplicate by direct LSC. The limit of detection (LOD) for the radioassays was 0.003 ppm for eggs and tissue, with the exception of egg white and liver (0.002 ppm). The total dosed radioactivity recovered was 103.0 and 105.7% for [phenyl-$^{14}$C] and [triazine-2-$^{14}$C]metsulfuron methyl, respectively, of which 102.9 and 105.3% of the administered dose was excreted. Radioactivity in eggs (<0.05-0.1%) and tissues (<0.05-0.1%) together accounted for ≤0.2%.

The TRR in eggs and edible tissues are summarized in Table 1. With the exception of [phenyl-$^{14}$C]-labeled egg whites, in which residues peaked on Day-2 at 0.047 ppm, $^{14}$C-residues in eggs increased throughout the dosing period peaking on Day-5 at 0.005-0.021 ppm in yolks, and 0.037 ppm in [triazine-2-$^{14}$C]-labeled egg whites. The study report stated that the [phenyl-$^{14}$C] Day-2 sample may have been contaminated by a small amount of excreta, and the HPLC profile for the sample provides further evidence supporting this assertion. The concentrations of $^{14}$C-residues in [phenyl-$^{14}$C]-labeled tissues, <0.01 ppm except liver at 0.013 ppm, were lower than those found in [triazine-2-$^{14}$C]-labeled tissues. $^{14}$C-Residues in [triazine-2-$^{14}$C]-labeled tissues were highest in skin (0.036 ppm), followed by liver and muscle (0.021-0.025 ppm), and lowest in fat (0.003 ppm).

Table 1. Total radioactive residues in eggs and edible tissues of hens dosed for 5 days with [phenyl-UL-$^{14}$C] or [triazine-2-$^{14}$C]metsulfuron methyl at ~12 ppm/day. [a]

| Matrix | Sampling Interval (Study Day) | Total Radioactive Residues (ppm) [b] | |
|---|---|---|---|
| | | [Phenyl-UL-$^{14}$C] | [Triazine-2-$^{14}$C] |
| Egg white | 1 | 0.032 | 0.014 |
| | 2 | **0.047** [c] | 0.019 |
| | 3 | 0.005 | 0.030 |
| | 4 | 0.006 | 0.034 |
| | 5 | 0.011 | **0.037** |
| Egg yolk | 1 | 0.003 | 0.005 |
| | 2 | 0.003 | 0.005 |
| | 3 | <0.003 | 0.011 |
| | 4 | 0.003 | 0.018 |
| | 5 | **0.005** | **0.021** |
| Breast muscle | 5 | <0.003 | 0.024 |
| Thigh muscle | | <0.003 | 0.021 |
| Skin | | 0.008 | 0.036 |
| Fat | | <0.003 | 0.003 |
| Liver | | 0.013 | 0.025 |

[a] Equivalent to ~120x the maximum theoretical dietary burden (MTDB) for poultry (0.1 ppm).

[b] Expressed in [$^{14}$C]metsulfuron methyl equivalents; data are the means of triplicate analyses of pooled samples from five hens per dose group.

[c] **Bolded** values represent maximum values in egg matrices. The study report stated that the [phenyl-$^{14}$C] Day-2 sample may have been contaminated by a small amount of excreta. The HPLC profile for the sample provides further evidence for this assertion.

## Extraction and hydrolysis of residues

*[Phenyl-UL-$^{14}$C]-labeled samples.* TRR in muscle, skin, fat and egg yolks were low (<0.003-0.008 ppm) and were not further analyzed. $^{14}$C-Residues in liver were extracted twice with methanol (MeOH):water (1:1, v/v), centrifuged, decanted, and combined. $^{14}$C-Residues in the combined methanolic extract (47.4%TRR, 0.006 ppm) were concentrated, partitioned with hexane, and the concentrated aqueous fraction was analyzed by HPLC; there were no significant $^{14}$C-residues in the hexane fraction, and it was not further analyzed. Further extraction of the post-extraction solids from liver (34.6%TRR, 0.004 ppm) using methylene chloride ($CHCl_2$) failed to release additional radioactivity. $^{14}$C-Residues in egg white were sequentially extracted with water and MeOH:water (1:1, v/v), combined, concentrated, and analyzed by HPLC. Unextracted $^{14}$C-residues accounted for 1.3% of the TRR (0.001 ppm) in egg white, and were not further analyzed.

*[Triazine-2-$^{14}$C]-labeled samples.* TRR were 0.003 ppm in fat, and were not further analyzed. $^{14}$C-Residues in liver, muscle (breast and thigh), skin, and egg yolk were extracted with MeOH:$CHCl_2$:2M ammonium carbonate (MMA solution; 3:4:1, v/v/v), centrifuged, concentrated, and partitioned with hexane. $^{14}$C-residues in the aqueous fraction were concentrated, and analyzed by HPLC; the hexane fractions contained little radioactivity (≤0.004 ppm), and were not further analyzed. $^{14}$C-Residues in egg whites were extracted in a similar manner as described for yolk, except MeOH was added to the initial extract to precipitate proteins, and no hexane wash was conducted; the extract was centrifuged, concentrated, and analyzed by HPLC. After protein precipitation and concentration, the fraction contained 80% of the TRR (0.030 ppm), a level not substantially different from the initial extract (83.1%TRR, 0.031). Unextracted $^{14}$C-residues in egg and tissues and were insignificant (≤8.3%TRR, ≤0.002 ppm), and were not further analyzed. The distribution of radioactivity following the extraction of residues from eggs and poultry tissues is presented in Tables 2 and 3.

$^{14}$C-Residues in [phenyl-$^{14}$C] and [triazine-2-$^{14}$C] excreta, which accounted for virtually all of the dosed radioactivity, were extracted using acetonitrile/water or MMA solution, respectively, and partitioned with hexane, $CHCl_2$, and/or MMA solution; the extractable $^{14}$C-residues remained exclusively in the aqueous fractions (>89%) which were subsequently analyzed by HPLC.

Table 2. Distribution of radioactivity after extraction of residues from eggs and tissues of hens dosed for 5 days with **[phenyl-UL-$^{14}$C]** metsulfuron methyl at ~12 ppm/day (~120x the MTDB for poultry).

| Fraction | Egg White (0.047 ppm) [a] | | Liver (0.013 ppm) | |
|---|---|---|---|---|
| | % TRR | ppm | % TRR | ppm |
| MeOH/$H_2O$ | 84.0 [b] | 0.040 | 47.4 | 0.006 |
| Hexane | NA [c] | -- | NR [d] | -- |
| Post-extraction solids | 1.3 | 0.001 | 34.6 | 0.004 |
| $CHCl_2$ | NA | -- | NR [d] | -- |
| Unextracted | 1.3 | 0.001 | 34.6 | 0.004 |

[a] TRR are for composite samples from the five hens in each group. Eggs collected on Day-2 were used.
[b] Fraction analyzed by HPLC.
[c] NA = Not applicable; fraction not produced.
[d] NR = Not reported but described as insignificant.

Table 3. Distribution of radioactivity following extraction of residues from eggs and tissues of hens dosed for 5 days with [**triazine-2-$^{14}$C**]metsulfuron methyl at ~12 ppm/day (~120x the MTDB for poultry).

| Fraction | Egg white (0.037 ppm)[a] | | Egg yolk (0.021 ppm)[a] | | Liver (0.025 ppm) | | Muscle (0.024 ppm)[b] | | Skin (0.036 ppm) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | % TRR | ppm | % TRR | ppm | % TRR | ppm | % TRR | ppm | % TRR | ppm |
| MMA[c] Solution | 83.1 | 0.031 | 93.5 | 0.020 | 89.5 | 0.022 | 77.9 | 0.019 | 75.0 | 0.027 |
| Aqueous | 80.0[d] | 0.030 | 76.0[e] | 0.016 | 67.3[d] | 0.017 | 67.5[d] | 0.016 | 62.3[d] | 0.022 |
| Hexane | NA[f] | -- | 16.5 | 0.004 | 13.9 | 0.004 | 0.9 | <0.001 | 1.6 | <0.001 |
| Unextracted | 5.2 | 0.002 | 2.6 | 0.001 | 8.3 | 0.002 | 1.4 | <0.001 | 2.7 | 0.001 |

[a] TRR are for composite samples from the five hens in each group. Eggs collected on Day-5 were used.
[b] Results for breast muscle. Similar extraction results were achieved for thigh muscle; the extract was not further analyzed.
[c] Methanol:methylene chloride:2M ammonium carbonate (3:4:1, v/v/v)
[d] Fraction analyzed by HPLC.
[e] Due to difficulties concentrating the sample (e.g., precipitation of solids and excessive viscosity), the fraction was not analyzed further.
[f] NA = Not applicable; no such fraction.

Characterization and Identification of residues

Radioactive residues in solvent extracts and fractions were analyzed using a Zorbax® Rx-C18 HPLC column with a mobile phase gradient of water with 0.1% phosphoric acid to acetonitrile with 0.1% phosphoric acid. $^{14}$C-Residues were detected using an in-line radioactivity detector and by LSC of collected fractions, and unlabeled reference compounds were detected using a UV absorbance detector (200-300 nm). The LOD for parent and metabolites in edible tissues was 0.0002-0.0005 ppm. Two reference standards, parent and *O*-desmethyl metsulfuron methyl, were used for comparison.

Parent compound and its minor metabolite *O*-desmethyl metsulfuron methyl were identified as comprising 88-91% and 2-4% of the TRR in excreta (both labels), respectively. Confirmation of the identity of parent compound and *O*-desmethyl metsulfuron methyl isolated from excreta of hens (both labels) was obtained by HPLC analyses using a PRP-1® HPLC column operating under conditions similar to the primary method described above.

Summaries of the identification/characterization of $^{14}$C-residues in tissues and egg from hens dosed with [phenyl-UL-$^{14}$C]- or [triazine-2-$^{14}$C]metsulfuron methyl are presented in Table 4. The chemical names and structures of metsulfuron methyl and its metabolites in poultry are depicted in Attachment 1 (Figure A).

Parent metsulfuron methyl was the principle component of the residue in [triazine-2-$^{14}$C]-labeled tissues, accounting for 8.6% of the TRR (0.001 ppm) in liver, 57.2% of the TRR (0.013 ppm) in

skin, and 14.2% of the TRR (0.004 ppm) in egg white. Parent was detected in [phenyl-$^{14}$C]-labeled egg white (88.0%TRR, 0.034 ppm), however, contamination of the sample with excreta is suspected. In addition to parent, the aqueous fraction of [triazine-2-$^{14}$C]-labeled liver, muscle, skin, and egg white contained multiple polar to moderately polar components which eluted as broad regions of radioactivity (each accounting for 35-85% of the TRR(≤0.022 ppm).

Proposed metabolic pathway

The petitioner proposes that parent metsulfuron methyl is excreted largely unchanged, and a minor portion is metabolized to *O*-desmethyl metsulfuron methyl.

Storage stability

Samples of tissues, egg, and excreta were stored frozen (-20°C) prior to and after TRR determinations, which were performed at Battelle, Columbus, OH within 6 days of sacrifice. After ~1 month of frozen storage, the samples were shipped on dry ice to Dupont, Wilmington, DE, where the samples were stored frozen prior to extraction. Extraction occurred within 163-205 days for tissue/egg samples analyzed by HPLC; definitive analyses of the select tissue/egg samples were performed within 2 weeks of extraction (~7 months of sacrifice). The HPLC profiles of the $^{14}$C-residues were similar for the tissues and egg samples extracted before or after 6 months, except for the minor differences in [phenyl-$^{14}$C]-labeled egg white, for which contamination was suspected. These data indicate that residues of [$^{14}$C] metsulfuron methyl were stable for the duration of the study; no additional storage stability data are required to support the hen metabolism study.

Conclusions: The nature of metsulfuron methyl residues in poultry is adequately understood. Overall, >86% of the TRR in tissues and eggs was adequately identified or characterized. Solvent extraction released 75-94% of the TRR from tissues and egg, except for [phenyl-$^{14}$C]-labeled liver, from which 47.4% of the TRR was extracted. Most of radioactivity remained in aqueous extracts, which were subsequently analyzed by HPLC provided they contained $^{14}$C-activity >0.01ppm. $^{14}$C-Residues in organosoluble/unextracted fractions (≤0.004 ppm) were not further analyzed. Parent metsulfuron methyl was the principle component of the residue in [triazine-2-$^{14}$C]-labeled tissues, accounting for 8.6% of the TRR (0.001 ppm) in liver, 57.2% of the TRR (0.013 ppm) in skin, and 14.2% of the TRR (0.004 ppm) in egg white. A high level of parent was detected in [phenyl-$^{14}$C]-labeled egg white (88.0%TRR, 0.034 ppm); however, contamination of the sample with excreta is suspected. In addition to parent, the aqueous fraction of [triazine-2-$^{14}$C]-labeled liver, muscle, skin, and egg white contained multiple polar to moderately polar components which eluted as broad regions of radioactivity (each accounting for 35-85% of the TRR(≤0.022 ppm).

Table 4. Characterization and identification of $^{14}$C-residues in eggs and tissues from hens dosed with **[triazine-2-$^{14}$C]**metsulfuron methyl at ~12 ppm/day (~120x the maximum theoretical dietary burden for poultry).

| Component | Liver (0.025 ppm) | | Muscle (0.024 ppm) | | Skin (0.036 ppm) | | Egg White (0.037 ppm) | |
|---|---|---|---|---|---|---|---|---|
| | % TRR | ppm | % TRR | ppm | % TRR | ppm | % TRR | ppm |
| Metsulfuron methyl | 8.6 | 0.001 | ND [a] | -- | 57.2 | 0.013 | 14.2 (88.0) [b] | 0.004 (0.034) |
| Unknown aqueous-soluble HPLC Peaks [c] | 80.2 | 0.014 | 84.9 | 0.014 | 35.0 | 0.008 | 75.8 | 0.022 |
| Hexane-soluble | 13.9 | 0.004 | 0.9 | <0.001 | 1.6 | <0.001 | NA [d] | -- |
| **Total identified or characterized** | **102.7** | **0.02** | **85.8** | **0.01** | **93.8** | **0.02** | **90.0 (88.0)** | **0.03 (0.034)** |
| Unextracted | 8.3 | 0.002 | 1.4 | <0.001 | 2.7 | 0.001 | 5.2 | 0.002 |

[a] ND = not detected.

[b] Values for Day-2 [phenyl-UL-$^{14}$C]-labeled egg white are shown in parentheses. As noted above, sample contamination with excreta was suspected, as the $^{14}$C-residue concentration was unusually high compared to egg samples from other days.

[c] Consist of multiple polar to moderately polar components which eluted as broad regions of radioactivity at retention times ($R_t$) of 4.4-17.6 minutes (each @≤0.022 ppm). The $R_t$ for metsulfuron methyl was ~38 minutes.

[d] NA = Not applicable; no such fraction.

## OPPTS GLN 860.1340: Residue Analytical Methods

In conjunction with the crop field trial and storage stability studies on sorghum (MRIDs 44155601 and 44477801), the petitioner submitted a description and method validation data for a HPLC/UV method (Morse Laboratories SOP # METH-82, Rev. No. 2) entitled, "Determination of Metsulfuron Methyl, Its Hydroxy Metabolite and Its Glucose Conjugate Metabolite in Sorghum Matrices." The method combines in a single method procedures similar to those used to determine residues of metsulfuron methyl in earlier residue studies (PP#3F4215, DP Barcode D1921296, M. Flood, 6/7/94). The method is summarized below. Adequate methods are available for enforcement of tolerances for residues of metsulfuron methyl in/on plant and animal commodities. PAM Vol. II lists Methods I and III which are respectively capable of determining residues of metsulfuron methyl *per se* (LOQ = 0.02 ppm for wheat grain; 0.05 ppm for forage and straw) and combined Metabolites A and A1 (LOQ = ppm for grain and forage; 0.1 ppm for straw); Method II determines parent compound in ruminant tissues and milk to a lower limit of 0.02-0.05 ppm. Recoveries of metsulfuron methyl under FDA Multiresidue Protocols are "not likely" (Pestrak, December, 1989).

Briefly, residues of metsulfuron methyl in/on sorghum grain, forage, and stover samples are extracted with methanol:0.01 M $K_2HPO_4$ buffer (25:75, v/v; pH 7.5), centrifuged, and adjusted to pH 6.0 with 10% phosphoric acid ($H_3PO_4$) solution. Residues of the glucose conjugate (Metabolite A) are hydrolyzed to 4-OH-metsulfuron methyl (Metabolite A1) by the addition of β-glucosidase (at 37°C for 1 hour). The residues are diluted with water, adjusted to pH 3 with 10% $H_3PO_4$, partitioned into dichloromethane, and concentrated to dryness. The residues are then reconstituted in methanol:0.01 M $K_2HPO_4$ buffer (7:93, v/v; pH 6.0), cleaned up by HPLC, and analyzed using reverse-phase HPLC with $C_8$- (grain) or phenyl- (forage and stover) columns with UV detection at 254 nm. The LOQ for residues of metsulfuron methyl *per se* is 0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage. The LOQ for the combined residues of Metabolites A1 and A, determined as Metabolite A1, is 0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage.

Method recovery data are presented in Table 5. For method validation, control samples of sorghum grain, forage, or stover were fortified with both metsulfuron methyl and Metabolite A1 at 0.05-0.25 ppm, or Metabolite A at 0.07-0.25 ppm. Overall method recoveries of metsulfuron methyl, Metabolite A1, and Metabolite A from each matrix were 69-104%, 62-105%, and 64-104%, respectively. As several recoveries for each analyte from stover were <70% at the lowest fortification level (0.05/0.07 ppm), the petitioner set the LOQ for residues of each analyte in/on stover at 0.1 ppm. For concurrent method recoveries, control samples were fortified with both metsulfuron methyl and Metabolite A1, or Metabolite A alone, each at 0.05-0.14 ppm. Overall recoveries of each analyte and matrix were 67-93%, with one unacceptable recovery (67%) for Metabolite A at the 0.14 ppm fortification level; however, the petitioner noted that extraction difficulties with grain samples from the crop field trials warranted an increase in the stated LOQ for residues of metsulfuron methyl and Metabolite A1 to 0.1 ppm. Apparent residues of each analyte were below the LOQ (<0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage). Sample calculations and chromatograms were submitted. Sample analyses were performed by Morse Laboratories, Sacramento, CA.

Conclusions: The HPLC/UV method (Morse Laboratories SOP # METH-82, Revision No. 2) used to determine residues of metsulfuron methyl and metabolites in/on grain sorghum RACs is adequate for data collection purposes. Adequate method validation data were submitted. The validated LOQ for metsulfuron methyl *per se* is 0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage. The combined LOQ for residues of Metabolite A1 (4-OH-metsulfuron methyl) and Metabolite A (metsulfuron methyl glucose conjugate), determined as Metabolite A1, is 0.1 ppm in/on grain and stover, and 0.05 ppm in/on forage.

The Agency has previously concluded that adequate methods are available for enforcement of tolerances for residues of metsulfuron methyl in/on plant and animal commodities. PAM Vol. II lists Methods I and III which are respectively capable of determining residues of metsulfuron methyl *per se* and the combined residues Metabolites A and A1 in/on wheat RACs; Method II determines metsulfuron methyl in ruminant tissues and milk. Metsulfuron methyl is not recovered by FDA Multiresidue Protocols.

Table 5. Method recoveries from control samples fortified with residues of metsulfuron methyl using the HPLC/UV method SOP# METH-82 (Revision No. 2).

| Analyte | Commodity | Fortification level (ppm) | # of Samples | % Recovery | |
|---|---|---|---|---|---|
| | | | | Range [a] | Avg ± SD |
| **Method Validation Recoveries** | | | | | |
| Metsulfuron methyl | Forage | 0.05-0.25 | 9 | 92-104 | 97 ±4 |
| | Grain | 0.05-0.25 | 9 | 71-94 | 86 ±8 |
| | Stover | 0.05-0.25 | 9 | 69-93 (1) | 82 ±8 |
| Metabolite A1 | Forage | 0.05-0.25 | 9 | 89-105 | 96 ±5 |
| | Grain | 0.05-0.25 | 9 | 76-104 | 93 ±10 |
| | Stover | 0.05-0.25 | 9 | 62-102 (2) | 80 ±13 |
| Metabolite A | Forage | 0.07-0.25 | 9 | 74-86 | 81 ±4 |
| | Grain | 0.07-0.25 | 9 | 79-104 | 89 ±9 |
| | Stover | 0.07-0.25 | 9 | 64-85 (5) | 73 ±8 |
| **Concurrrent Recovery** | | | | | |
| Metsulfuron methyl | Forage | 0.05 | 2 | 85, 77 | 79±5 |
| | Grain | 0.10 | 2 | 76, 80 | |
| | Stover | 0.10 | 2 | 72, 86 | |
| Metabolite A1 | Forage | 0.05 | 2 | 82, 81 | 77±7 |
| | Grain | 0.10 | 2 | 76, 84 | |
| | Stover | 0.10 | 2 | 72, 65 | |
| Metabolite A | Forage | 0.07 | 2 | 71, 78 | 78±9 |
| | Grain | 0.07 | 2 | 79, 93 | |
| | Stover | 0.14 | 2 | 67, 82 | |

[a] Value in parenthesis is the number of recoveries outside the acceptable range (70-120%).

## OPPTS GLN 860.1380: Storage Stability Data

In a previous review of residue data on grain sorghum (PP#3F4215, DP Barcode D191296, M. Flood, 6/7/94), the Agency required data demonstrating the storage stability of metsulfuron methyl Metabolites A and A1 in frozen grain sorghum RACs for ≥7.5 months; the available storage stability data indicate that fortified residues of metsulfuron methyl *per se* are stable under frozen storage conditions for up to ~5 years in/on wheat grain, and for up to ~4 years in wheat forage and straw (PP#1F4029, DP Barcode D171707, J. Stokes, 4/28/93). In addition, data depicting the storage stability of metsulfuron methyl in extracts held under the storage intervals and conditions of the study were required as extracts were stored for up to 6 weeks before analysis for metsulfuron methyl *per se*.

In response, the petitioner has submitted data depicting the frozen storage stability of metsulfuron methyl and its metabolites, Metabolite A1 (4-hydroxy metsulfuron methyl) and Metabolite A

(metsulfuron methyl glucose conjugate), in/on grain sorghum matrices stored for up to 9 months at -20 C. In addition, the petitioner submitted data depicting storage stability of metsulfuron methyl and Metabolite A1 in extracted samples of grain sorghum matrices refrigerated at 1-8°C for up to 8 weeks. The results from these studies are reported in:

44477801 Trubey, R. (1998) Freezer Storage Stability of Metsulfuron Methyl and Metabolites in Grain Sorghum (Forage, Grain, and Fodder): Lab Project Number: AMR 3456-95: ML95-0532-DUP: METH-82. Unpublished study prepared by DuPont Agricultural Products and Morse Labs., Inc. 183 p. {OPPTS 860.1380}

In the frozen storage stability study, control samples of each grain sorghum matrix were fortified with metsulfuron methyl and 4-hydroxy metsulfuron methyl, each at 0.20 ppm using a mixed solution containing both analytes, or with metsulfuron methyl glucose conjugate at 0.20 ppm, and stored frozen at -20 ± 5 C. At each sampling interval (0 days and 2, 6, and 9 months), a control sample, a freshly fortified sample, and two stored fortified samples were analyzed for each analyte matrix using the HPLC/UV method described above. Residues of each analyte were <LOQ in/on all control samples. The results of the frozen storage stability study are shown in Table 6.

For the refrigeration storage stability study on extracts, the 6-month sample prepared for the frozen storage stability was extracted and divided into two subsamples. One sub-sample was analyzed immediately as the 6-month frozen storage stability sample as well as the 0-day refrigeration storage stability extraction sample. The remaining subsamples were stored refrigerated and analyzed after 8 weeks. At each sampling interval, a single control and freshly fortified sample, and two stored fortified samples were analyzed for each matrix using the HPLC/UV method described above. Additionally, a second control and freshly fortified sample were analyzed at 8 weeks to double check the method performance. Metsulfuron methyl glucose conjugate stability was not evaluated as it was expected to convert to 4-hydroxy metsulfuron methyl during refrigeration. Residues of each analyte were <LOQ in all control samples.

All samples were analyzed by Morse Laboratories, Inc., Sacramento, CA. Adequate representative chromatograms and data worksheets were provided. The results of the refrigeration storage stability study are presented in Table 7.

*Conclusions*: The storage stability data are adequate and indicate that residues of metsulfuron methyl and its metabolites, A1 and A, are stable in sorghum forage, grain, and stover for up to 9 months at -20±5°C. In addition, metsulfuron methyl and A1 are stable in refrigerated extracts of sorghum forage, grain, and stover for up to 8 weeks at 1-8°C. These data support the residue data submitted for the permanent tolerance petition for residues of metsulfuron in/on grain sorghum.

Table 6. Storage stability of residues of metsulfuron methyl and its metabolites fortified in control samples of grain sorghum matrices at 0.20 ppm and stored frozen at -20 ± 5°C for up to 9 months.

| Matrix | Storage Interval (months) | Fresh Fortification % Recovery [a] | Stored Sample % Recovery [b] | Stored Sample Corrected % Recovery [c] |
|---|---|---|---|---|
| **Metsulfuron Methyl** | | | | |
| Forage | 0 | 103 | 95 | --- [d] |
| | 2 | 103 | 104 | 101 |
| | 6 | 90 | 94 | 104 |
| | 9 | 106 | 104 | 98 |
| Grain | 0 | 84 | 82 | --- |
| | 2 | 73 | 78 | 107 |
| | 6 | 75 | 69 | 92 |
| | 9 | 80 | 90 | 113 |
| Stover | 0 | 84 | 89 | --- |
| | 2 | 70 | 77 | 110 |
| | 6 | 81 | 80 | 99 |
| | 9 | 84 | 87 | 104 |
| **A1** (4-Hydroxy Metsulfuron Methyl) | | | | |
| Forage | 0 | 100 | 92 | --- |
| | 2 | 105 | 100 | 95 |
| | 6 | 90 | 89 | 99 |
| | 9 | 105 | 101 | 96 |
| Grain | 0 | 91 | 85 | --- |
| | 2 | 74 | 77 | 104 |
| | 6 | 74 | 66 | 89 |
| | 9 | 82 | 90 | 110 |
| Stover | 0 | 85 | 90 | --- |
| | 2 | 48 | 75 | 156 |
| | 6 | 78 | 73 | 94 |
| | 9 | 89 | 87 | 98 |
| **A** (Metsulfuron Methyl Glucose Conjugate) | | | | |
| Forage | 0 | 93 | 80 | --- |
| | 2 | 92 | 89 | 97 |
| | 6 | 91 | 78 | 86 |
| | 9 | 93 | 92 | 99 |
| Grain | 0 | 92 | 95 | --- |
| | 2 | 80 | 70 | 88 |
| | 6 | 68 | 67 | 99 |
| | 9 | 85 | 96 | 113 |
| Stover | 0 | 81 | 89 | --- |
| | 2 | 83 | 62 | 75 |
| | 6 | 69 | 49 | 71 |
| | 9 | 99 | 84 | 85 |

[a] Single fresh fortification recovery.
[b] Average of two stored sample recoveries.

[c] Calculated by the reviewer by dividing the average stored sample recovery by the fresh fortification recovery.
[d] --- = Not applicable

Table 7. Storage stability of residues of metsulfuron methyl and A1 in extracts from control samples of grain sorghum matrices fortified at 0.20 ppm, stored refrigerated at 1-8°C for up to 8 weeks.

| Matrix | Storage Interval (weeks) | Fresh Fortification % Recovery [a] | Stored Sample % Recovery [b] | Stored Sample Corrected % Recovery [c] |
|---|---|---|---|---|
| **Metsulfuron Methyl** | | | | |
| Forage | 0 | 90 | 94 | --- [d] |
| | 8 | 89 | 100 | 112 |
| Grain | 0 | 75 | 69 | --- |
| | 8 | 94 | 88 | 94 |
| Stover | 0 | 81 | 80 | --- |
| | 8 | 89 | 89 | 100 |
| **A1** (4-Hydroxy Metsulfuron Methyl) | | | | |
| Forage | 0 | 90 | 89 | --- |
| | 8 | 81 | 90 | 111 |
| Grain | 0 | 74 | 66 | --- |
| | 8 | 94 | 86 | 91 |
| Stover | 0 | 78 | 73 | --- |
| | 8 | 75 | 84 | 112 |

[a] Single fresh fortification recovery at 0 days and average of two recoveries at 8 weeks.
[b] Average of two stored sample recoveries.
[c] Calculated by the reviewer by dividing the average of two stored sample recoveries by the fresh fortification recovery.
[d] --- = Not applicable.

## OPPTS GLN 860.1500: Magnitude of the Residue - Plants

Grain sorghum

DuPont submitted data from two field trials conducted during 1995 in KS and OK depicting residues of metsulfuron methyl and its metabolites A1 and A (4-OH-metsulfuron methyl and its glucose conjugate) in/on grain sorghum. The results are reported in:

44155601 Trubey, R. (1996) Magnitude of Residues of Metsulfuron Methyl in Grain Sorghum Following Application of Ally Herbicide at Maximum Label Rate Maximum Label Rates: Lab Project Number: AMR 3244-94: ML95-0520-DUP: METH-82. Unpublished study prepared by DuPont Agricultural Prods. and Morse Labs, Inc. 149 p.

At each trial location, two tests were performed in which metsulfuron methyl (60% DF) was applied once as a broadcast foliar application to grain sorghum at 0.03 or 0.06 oz ai/A/season (1

or 2x the proposed maximum rate). Applications were made using ground equipment with 15.3-20 gal/A of water to grain sorghum at the 7- to 10-leaf stage (14-19 inches tall). A single control and duplicate treated samples of forage and mature grain and stover were collected 31-39 or 66-88 days posttreatment, respectively. Samples were placed in frozen storage at the test locations within 4 hours, and were shipped within the next 14-71 days by ACDS freezer truck (on dry ice) to Morse Laboratories, Sacramento, CA, where they were held frozen (-20±5°C) prior to analysis. Samples were stored frozen for up to 212 days (~7 months) from harvest to analysis. The submitted storage stability data supports the subject residue data.

Residues of metsulfuron methyl and its metabolites were determined using HPLC/UV method SOP# METH-82 (Rev. No. 2) described in the Residue Analytical Methods section. Adequate concurrent recoveries of each analyte were obtained from grain sorghum matrices. Apparent residues of each analyte were <LOQ in/on each of four untreated grain, forage, and stover samples.

Residues of metsulfuron methyl *per se*, and the combined residues of metabolites A1 and A determined as A1, were not quantifiable (<0.1 ppm for grain and stover; <0.05 ppm for forage) in/on eight treated samples each of forage or mature grain and stover harvested 31-39 or 66-88 days, respectively, after treatment at up to 2x the proposed maximum rate.

Conclusions: The Agency has previously reviewed data (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94) from six field trials on grain sorghum conducted prior to 1992 in CA, KS, MO, NC, OK, and TX. Residues of metsulfuron methyl *per se* and the combined residues of its two metabolites were each below the respective LOQ (<0.05 ppm for grain; <0.1 for forage and stover) in/on all treated samples of forage or mature grain and stover harvested ~30 or 66-97 days after application of metsulfuron methyl (60% DF) at 0.03-0.06 oz ai/A/season (1 or 2x). The Agency subsequently concluded (PP#3F4215, DP Barcode 211879, M Flood, 4/4/95) that a regional registration for the use on sorghum might be obtained provided that the petitioner conduct two additional field trials in Region 8.

The submitted residue data from two field trials (four tests) on grain sorghum are adequate. Residues of metsulfuron methyl *per se* and its metabolites A1 and A (determined as A1) were not quantifiable (<0.1 ppm for grain and stover; <0.05 ppm for forage) in/on eight treated samples each of forage or mature grain and stover harvested 31-39 or 66-88 days, respectively, after treatment with metsulfuron methyl at 0.03 or 0.06 oz ai/A/season (1 or 2x).

The geographic representation of the data and the number of tests conducted are sufficient to support the proposed regional registration of metsulfuron methyl on grain sorghum. The petitioner has conducted a total of four trials at 1-2x the proposed maximum rate and minimum PHI on grain sorghum in Region 8. The submitted data are adequate to support the proposed tolerances with regional registration for residues of metsulfuron methyl in/on sorghum grain at 0.1 and sorghum forage and stover at 0.2 ppm. However, a revised Section F should be

submitted to include both the parent and metabolite in the tolerance expression as stated in 40 CFR: 180.428(a).

**OPPTS GLN 860:1520: Processed Food/Feed**

Based on a sorghum processing study, the Agency has previously concluded (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94) that metsulfuron methyl and its metabolites do not concentrate in grain sorghum processed commodities or aspirated grain fractions; therefore, no tolerances are required for residues in sorghum processed commodities.

**OPPTS GLN 860.1480: Meat/Milk/Poultry/Eggs**

The Agency has previously concluded that existing tolerances for residues in meat and milk will not be exceeded from the proposed use on sorghum grain, considering that it is unlikely to effect the maximum expected dietary burden of metsulfuron methyl residues for ruminants (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94).

Based on the calculated maximum theoretical dietary exposure for poultry (0.1 ppm), the ~12 ppm dose level used in the poultry metabolism studies discussed above reflect a 120x dose level. Considering the level of residues found in poultry commodities in the hen metabolism study at the 12 ppm dosing level, there is no reasonable expectation of finite residues being transferred to poultry tissues and egg from the proposed use of metsulfuron methyl on grain sorghum; therefore, tolerances for residues in poultry are not required at this time.

**OPPTS GLN 860.1850 and 860.1900: Confined/Field Accumulation in Rotational Crops**

Restrictions on rotational crop intervals were previously stated as: "Minimum rotation intervals from 1 to 22 months are specified explicitly for wheat, field corn, soybeans and cotton. For all other crops, the minimum rotation interval is 34 months" (PP#3F4215, DP Barcodes D191296 & D191298, M. Flood, 6/7/94). HED's policy no longer considers rotational crop intervals of greater than 12 months practical unless driven by phytotoxicity concerns. Therefore, the label can be amended to allow replanting of crops for which there are registered uses at any interval and for all other crops after 12 months unless the registrant wishes to retain the longer replant intervals due to phytotoxicity concerns.

Other Considerations:

There are no Mexican, Canadian, or Codex MRLs established for metsulfuron methyl on grain sorghum. Therefore there are no compatibility issues to be reconciled.

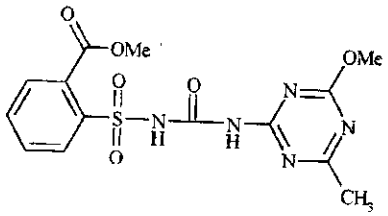
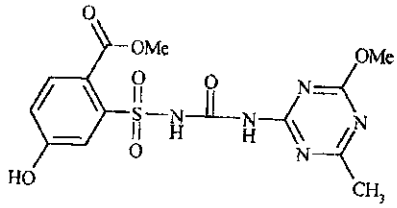
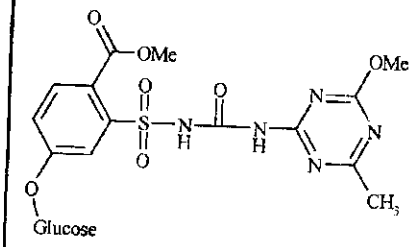
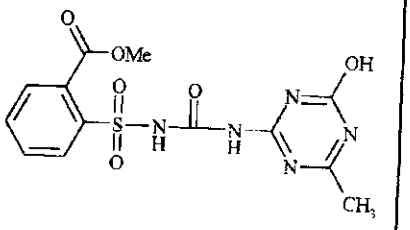
## AGENCY MEMORANDA CITED

DP Barcode: D171707 and D171709
Subject: PP#1F4029. Metsulfuron methyl in/on Wheat and Barley. Evaluation of analytical method and residue data.
From: J. Stokes
To: R. Taylor/A. Kocialski
Dated: 4/28/93
MRID(s): 42016501 to 42016505; 42016508; and 42080601

DP Barcode: D191296 and D191298
Subject: PP#3F4215. Metsulfuron-methyl (Ally®) for use in/on grain sorghum. Analytical methods and residue data.
From: M. Flood
To: R. Taylor/V. Walters
Dated: 6/7/94
MRID(s): 42759001 and 42759002

DP Barcode: D211881 and D211879
Subject: PP#3F4215. Metsulfuron-methyl (Ally®) for use in/on grain sorghum. DuPont's 12/16/94 response to CBTS' 6/7/94 memo.
From: M. Flood
To: R. Taylor/V. Walters
Dated: 4/4/95
MRID(s): None

Figure A. Metsulfuron-methyl and its metabolites in plants and poultry.

| Common Name/Chemical Name | Chemical Structure | Matrix |
|---|---|---|
| **Metsulfuron methyl**<br><br>(DPX-T6376)<br><br>Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino] sulfonyl]benzoate |  | Plants/Poultry |
| **4-Hydroxy metsulfuron methyl**<br><br>**Metabolite A1**<br><br>(IN-G7460)<br><br>Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino] sulfonyl] 4-hydroxybenzoate |  | Plants |
| **Metsulfuron methyl glucose conjugate**<br><br>**Metabolite A**<br><br>(IN-B9700)<br><br>Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino] sulfonyl]4-(β-D-glucopyranosyl)benzoate |  | Plants |
| ***O*-Desmethyl metsulfuron methyl**<br><br>(IN-B5067)<br><br>Methyl 2-[[[[(4-hydroxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino] sulfonyl]benzoate |  | Poultry |