CONFIDENTIAL

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

MAR 8 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: PP#3F04193. Permanent Tolerance Request for Use of MON 12000 (Halosulfuron) on Field Corn and Grain Sorghum (Milo). Evaluation of Analytical Method and Residue Data.
MRID#s: 426614-01 through -07 and 430426-01 and -02 (15 vol.)
DP Barcodes# **D189198, D198051**
CBTS# 11593, 13027
Section 3 Registration Request for the Following Products:
000524-UAT. MON 12000 Technical
DP Barcode# **D189189**
CBTS# 11591
000524-UAL. Permit® Herbicide
DP Barcode# **D189178**
CBTS# 11589
000524-UAA. Battalion® Herbicide
DP Barcode# **D189183**
CBTS# 11590
000524-UAI. Manage® Herbicide
DP Barcode# **D189195**
CBTS# 11592

From: G. Jeffrey Herndon, Chemist
Tolerance Petition Section II
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

G. Jeffrey Herndon

Through: Debra Edwards, Ph.D., Chief
Chemistry Branch I - Tolerance Support
Health Effects Division (H7509C)

Debra Edwards

To: Joanne Miller/Daniel Kenny, PM Team 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Albin Kocialski, Head
Registration Section
Chemical Coordination Branch
Health Effects Division (H7509C)

The petitioner, Monsanto Chemical Company, requests that permanent tolerances be established for the residues of the herbicide designated by the company code MON 12000, methyl 5-{[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonylaminosulfonyl}-3-chloro-1-methyl-1-H-pyrazole-4-carboxylate, and its metabolites determined as 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylic acid and expressed as parent equivalents, in/on the following raw agricultural commodities:

Corn,field

grain	0.1 ppm
forage	0.3 ppm
fodder	1.3 ppm

Grain Sorghum (milo)

grain	0.02 ppm
forage	0.07 ppm
stover	0.08 ppm
silage	0.14 ppm

Associated with these permanent tolerances, Monsanto has requested the following Section 3 Registrations:

MON 12000 technical grade active ingredient

Permit® Herbicide, a water dispersable granule formulation (MON 12037 without water soluble packaging, MON 12042 with water soluble packaging) for postemergence use in field corn, and use in grain sorghum.

Battalion® Herbicide, a water dispersable granule formulation (MON 12041) for preemergence use in field corn.

Manage® Herbicide, a wettable powder formulation (MON 12051 without water soluble packaging, MON 12039 with water soluble packaging) for use on turf.

Manage uses are non-food, are not under the purview of CBTS, and will not be reviewed in this memo.

This chemical is a member of the sulfonylurea class of herbicides and is being developed jointly by Monsanto Chemical Company and NISSAN Chemical Company of Japan. The technical grade active ingredients are designated by the company codes MON 12000 (Monsanto) and NC-319 (NISSAN).

MON 12000 is intended to control annual broadleaf weeds and nutsedge in corn, grain sorghum, and turf. In sorghum and turf, MON 12000 is applied post-emergence; in corn, it can be applied pre- and/or post-emergence. For pre-emergent applications in corn, it is

necessary to include the [redacted] The mode of action on MON 12000 is the inhibition of the plant enzyme aceto lactase synthetase, which is essential for the production of required amino acids in the plant. [redacted]

This is the first Section 3/permanent tolerance request for MON 12000. CBTS previously reviewed EUP and temporary tolerance requests for use of MON 12000 products on field corn (PP#2G4073, 000524-EUP-TO, 000524-EUP-TA). These requests were reviewed in memos by G.J. Herndon dated 7/30/92, 9/8/92, 11/12/92, 12/9/92, 1/21/93, 2/4/93, 3/11/93, 3/16/93, 3/17/93, 3/29/93, 5/6/93, 7/1/93, 9/28/93 and G.F. Kramer dated 8/30/93. In the memo of 3/29/93, CBTS recommended in favor of establishing temporary tolerances of field corn grain, forage, and fodder.

CBTS defers the product chemistry review of end-use products to Registration Division.

Note: Throughout this memo the terms "grain sorghum" and "milo" are used interchangeably

Conclusions

1. Data in this petition were not generated by Craven Laboratories.

2. The submitted product chemistry data are not sufficient to fulfill the requirements for this Section 3/permanent tolerance request. As outlined in Attachments I and II, additional data are required to satisfy 61-1, 61-2, 62-1, and 62-2.

3a. The proposed Permit® label lists various rates of product to use based on weed species and size. These rates were apparently intended to be used on field corn only, since they exceed the maximum proposed label rate for milo by 2X. Monsanto should move this section of the label to immediately follow the field corn directions (and precede the milo directions).

3b. Until the issue of the toxicity of the MON 12000 pyrazole moiety (i.e. 3-chlorosulfonamide acid) is resolved (see Conclusion 4d), the number of rotational crops allowed on the label, as well as the plantback intervals for these crops will need to be restricted. As noted in Conclusion 4f, Monsanto agreed that, until the TOX studies are completed, they would like to have target crop tolerances with an expiration date on corn and milo, and rotational crop tolerances on soybean and wheat only. **Provided that the requested DRES analysis indicates that CBTS can recommend in favor of a conditional registration (see Conclusion 10e)**, the tolerances, with an expiration date, for rotational crops would be based on the

limited field trials (3 sites per crop). Therefore, Monsanto will need to revise their proposed labels for Permit® and Battalion® by deleting the current language concerning rotational crops and add the following:

> Permit® or Battalion® treated milo or field corn fields may be rotated or replanted to milo, field corn, soybeans, or wheat (spring or winter) only. Do not replant or rotate to soybeans or wheat within 12 months of an application of Permit® or Battalion®. Corn or milo can be replanted in the same growing season provided the maximum rate of Permit® and/or Battalion® per season is not exceeded.

Otherwise, crop rotation/replanting to any crop other than corn and milo will need to be restricted.

4a. The nature of the residue in corn is adequately elucidated. The metabolism of MON 12000 in corn depends on the mode of application (post or preemergence). In all commodities except grain, the major residue from postemergence use was the unmetabolized parent compound. Chlorosulfonamide acid was the major metabolite found in grain from postemergence use, and in all commodities from preemergence use of MON 12000.

4b. Based on the analytical method, the residue from either use can be regulated as parent (MON 12000) and metabolites, determined as 3-chlorosulfonamide acid, and expressed as parent equivalents, which is how the residues were regulated in the EUP/temporary tolerance request for use on field corn (see memo of G.J. Herndon dated 7/30/92).

4c. Since that time, Monsanto has proposed to change the tolerance expression to include only the parent compound ("exempt" 3-CSA from the requirements of a tolerance) in order to avoid rotational crop tolerances (see Conclusion 10a).

4d. The issue was presented to the HED Metabolism Committee on 9/15/93. In that meeting, the committee concentrated on the results of the corn metabolism studies, the rat metabolism studies, and the rotational crop studies. The major pyrazole moiety metabolites of MON 12000 that were found in the corn metabolism study, 3-chlorosulfonamide acid and 3-chlorosulfonamide ester, were not found in the rat metabolism study.

As a result of the 9/15/93 meeting (see memo of G.J. Herndon dated 9/28/93), the Metabolism Committee decided that, due to the lack of toxicology data on the 3-CSA and 3-CSE metabolites, coupled with the fact that the results of both the field and confined rotational crop studies indicate that metabolites containing the pyrazole moiety may accumulate in harvested crops planted at an interval greater than one year, they would postpone making a

decision on which residue(s) should be regulated from the use of MON 12000 on corn pending the results of additional toxicology testing (90 day, developmental, and mutagenicity studies) using 3-chlorosulfonamide acid as the dosing material. Once the additional toxicology data are submitted and reviewed, another meeting of the HED Metabolism Committee will probably be necessary to address the question of which residue(s) to regulate. If the metabolite is of comparable or greater toxicity than the parent, it will need to be included in the tolerance for target and rotational crops.

4e. Until the additional toxicology data are submitted and reviewed (see Conclusion 4d.), the nature of the residue in plants will be regulated as parent (MON 12000) and metabolites, determined as 3-chlorosulfonamide acid, and expressed as parent equivalents (see Conclusion 8a for the complete expression).

4f. In a meeting held on 11/19/93 (see memo of G.J. Herndon dated 11/22/93), Monsanto explained that they are willing to perform the 3 requested toxicology studies on the metabolite, but would like the Agency to grant them a conditional registration while the studies are being conducted and reviewed. Until the studies are completed, Monsanto would like to have target crop tolerances with an expiration date on corn and milo, and rotational crop tolerances on soybean and wheat. Based on this, HED explained that we would need to make a DRES run to determine the % of the RfD that would be used assuming 100% crop treated and total residue (MON 12000 plus metabolites) for these 4 crops. If the results indicate acceptable risk, HED might be able to recommend in favor of a conditional registration with tolerances having an expiration date. The tolerances for rotational crops would be based on the limited field trials (3 sites per crop).

4g. In a memo from G.J. Herndon dated 11/24/93, CBTS requested a DRES analysis to determine the dietary risk associated with issuing a conditional registration and tolerances with expiration dates for use of MON 12000 on field corn and grain sorghum. The results from the DRES analysis are not yet available, and therefore no conclusions concerning the potential for a conditional registration can be drawn until the analysis is completed. A separate memo will follow.

5a. As noted in the 7/30/92 memo of G.J. Herndon, the nature of the residue in ruminants was determined to be adequately understood, **for the purposes of the requested EUP/temporary tolerance request where the regulation of animal commodities was not necessary.** In the tissues and milk of goats, the major extractable residue was the unmetabolized parent compound.

5b. Based on the results of the lactating cattle feeding study that was submitted as requested (see Conclusion 11a), the regulation of cattle, goats, hogs, horses, and sheep meat by-products is required for the current Section 3/permanent tolerance

request. Therefore, as outlined in the 11/12/92 memo of G.J. Herndon (review of a hen metabolism study), Monsanto was requested to address the following points before any future tolerances on livestock commodities were considered:

> i. In the HPLC analysis of the double-labeled hen metabolites, the registrant implies that the method is not able to separate or distinguish between aminopyrimidine and 4,6-dihydroxy MON 12000. The registrant is asked to comment on this, as well as how this might impact the goat metabolism study (MRID# 421394-06), since the results from this study do not indicate a potential coelution problem between aminopyrimidine and 4,6-dihydroxy MON 12000.
>
> ii. The registrant is asked to explain why the ratios of aminopyrimidine and 3-chlorosulfonamide ester vary in the goat and hen metabolism studies, when both apparently involve spiking MON 12000 onto blank liver samples. Shouldn't the ratios of aminopyrimidine to 3-chlorosulfonamide ester be about 1:1 in the hen study, similar to the results of the goat study?

5c. Tentatively (pending the outcome of the registrant's responses to Conclusion 5b), the nature of the residue in animals will be regulated as parent (MON 12000) and metabolites, determined as 3-chlorosulfonamide acid, and expressed as parent equivalents (similar to the plant expression).

5d. Based on the low residues of MON 12000 on corn grain and the low transfer of residues in the metabolism study, tolerances on poultry products are not required for this Section 3/permanent tolerance request for use of MON 12000 on corn and grain sorghum. However, if additional or different uses of MON 12000 result in the maximum residues in corn grain or another poultry feed item treated with MON 12000 to exceed 0.1 ppm, regulating poultry commodities may be necessary. In this case, CBTS will require additional characterization and identification of MON 12000 metabolites in the previously reviewed laying hen metabolism study. The additional requirements are outlined in Conclusions 5b, 5c, 5d, 5f, 5g, 5h in the memo of G.J. Herndon dated 11/12/92.

6a. The registrant submitted a proposed analytical method (RES-012-91) for analysis of MON 12000 residues in field corn RACs that was reviewed in conjunction with PP#2G4073 (see reviews of G.J. Herndon dated 7/30/92, 11/12/92, 12/9/92, 1/21/93, 2/4/93, 3/11/93, 3/16/93, 3/17/93, 7/1/93, and 10/7/93). RES-012-91 can be used to quantitate residues of MON 12000, MON 12000 acid, 3-chlorosulfonamide ester, and 3-chlorosulfonamide acid residues. The method cleaves any MON 12000 and MON 12000 acid residues to

residues of chlorosulfonamide acid and animopyrimidine. Since no aminopyrimidine residues have been found in field corn matrices, any animopyrimidine concentrations found correspond directly to the initial MON 12000 and MON 12000 acid concentrations. The amount of free 3-chlorosulfonamide acid and 3-chlorosulfonamide ester found in the samples is quantitated by subtracting the portion of the 3-chlorosulfonamide acid arising from the MON 12000/MON 12000 acid hydrolysis from the total 3-chlorosulfonamide acid residue obtained (The portion of 3-chlorosulfonamide acid arising from hydrolysis corresponds to the amount of aminopyrimidine found).

6b. The method underwent independent lab validation and Beltsville lab validation for field corn RACs. CBTS and the Beltsville lab concluded that RES-012-91 is adequate for enforcement. The methods used to analyze the processed corn fractions (RES-043-92), milo RACs (RES-012-91, version 2 and RES-026-92) and processed milo commodities (RES-045-92) are essentially the same as the RES-012-91.

6c. The results of the FDA multiresidue method testing of MON 12000 and 3-CSA have been sent to FDA and Beltsville (memo of G.J. Herndon dated 10/7/93).

6d. Based on the results of the lactating cattle feeding study that was submitted as requested (see Conclusion 11a), the regulation of cattle, goats, hogs, horses, and sheep meat by-products is required for the current Section 3/permanent tolerance request. Therefore, the registrant will need to submit a method for analyzing these meat by-products and the results from both lab and independent lab validation. The method will then be forwarded to the Beltsville lab for their validation. The meat by-products method must be validated by Beltsville before CBTS can recommend in favor of a Section 3/permanent tolerance request for use of MON 12000 on corn and milo.

7a. The available storage stability data are adequate to show that residues of **3-CSA** are stable in field corn RACs for up to 27 months. This covers the time period that the field corn residue samples used in support of this petition were stored (up to 20 months).

7b. The 6 month storage stability period for milo field samples would normally not be sufficient to cover the maximum 10 month period that the field residue samples used in support of this petition were stored. However, since milo and corn are closely related (they are in the same crop group) and 3-CSA has been shown to be stable in field corn RACs at intervals up to 27 months, this will not be a deficiency. The available storage stability data are adequate to show that residues of 3-CSA are stable over the time period that the milo field residue samples used in support of this petition were stored.

7

7c. The results from the aminopyrimidine recoveries indicate much more variability and less stability than the 3-CSA residues over the same time period. If the need for analyzing aminopyrimidine arises, the variability in the storage stability recoveries will need to be reexamined.

8a. Based on the best correlation between the worst case proposed use (maximum rate and shortest PHI) and the field trial data, the registrant will need to propose a new Section F, that reads as follows:

> Monsanto requests that permanent tolerances be established for the residues of methyl 5-{[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonylaminosulfonyl}-3-chloro-1-methyl-1-H-pyrazole-4-carboxylate and its metabolites determined as 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylic acid and expressed as parent equivalents, in/on the following raw agricultural commodities:
>
> | | |
> |---|---|
> | Corn, field | |
> | grain | 0.1 ppm |
> | forage | 0.3 ppm |
> | fodder | 1.5 ppm |
> | Sorghum, grain | |
> | grain | 0.1 ppm |
> | forage | 0.1 ppm |
> | fodder/stover | 0.1 ppm |
>
> Note: Tolerances for sorghum silage and hay are no longer necessary. The commodities will be deleted in the forthcoming revised Table II. Silage residues will be covered by the tolerance on forage.

8b. As noted in Conclusions 10e and 11a, the registrant will also need to propose rotational crop and meat by-product tolerances.

9. Based on submitted corn and milo processing studies, CBTS concludes that tolerances of 0.1 ppm on field corn grain and milo grain should be adequate to cover the residues on the regulated processed corn and milo commodities as a result of the proposed use.

10a. The results of both the field and confined rotational crop studies indicate that metabolites containing the pyrazole moiety may accumulate in harvested crops planted at an interval greater that one year. As noted in G.F. Kramer's review of 8/30/93, if the HED Metabolism Committee determines that MON 12000 metabolites containing the pyrazole moiety need to be regulated, the presence of these residues in all rotational crops studied

(except lettuce) indicates that extensive field trials will be required to set tolerances for each crop group for which crop rotation will be permitted.

10b. In their meeting held on 9/15/93, the HED Metabolism Committee concluded that no new rotational crop residue data will be required until the additional TOX data requested are submitted and reviewed (see memo of G.J. Herndon dated 9/28/93). However, in a meeting held on 11/19/93 (see memo of G.J. Herndon dated 11/22/93), Monsanto explained that they would initiate additional field rotational crop studies now, rather than wait until the additional toxicology results are reviewed.

10c. see Conclusion 4f.

10d. In a memo from G.J. Herndon dated 11/24/93, CBTS requested a DRES analysis to determine the dietary risks associated with issuing a conditional registration and tolerances with expiration dates for use of MON 12000 on field corn and grain sorghum. The residue values to be used in the DRES analysis are:

RAC	Maximum Residue (total)
field corn grain	0.1 ppm
sorghum grain	0.02 ppm
soybean seed	0.5 ppm
wheat grain	0.1 ppm

The residue levels for the corn and sorghum would apply to target and rotational crop uses; the soybean and wheat residue levels apply to rotational crop uses only.

10e. The results from the DRES analysis are not yet available, and therefore no conclusions concerning the potential for a conditional registration can be drawn until the analysis is completed. A separate memo will follow. However, if the DRES memo indicates that HED can recommend in favor of a conditional registration, the registrant will need to provide a new Section F that reads as follows:

> Monsanto requests that permanent tolerances be established for the indirect or inadvertent residues of methyl 5-{[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonylaminosulfonyl}-3-chloro-1-methyl-1-H-pyrazole-4-carboxylate and its metabolites determined as 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylic acid and expressed as parent equivalents, in/on the following raw agricultural commodities when present therein as a result of the application of halosulfuron to field corn and/or grain sorghum:

Soybean		
	seed	0.5 ppm
	forage	0.5 ppm
	hay	0.5 ppm
Wheat		
	grain	0.1 ppm
	forage	0.1 ppm
	straw	0.2 ppm

Otherwise, crop rotation/replanting to any crop other than corn and milo will need to be restricted.

11a. Based on Tables 12 and 13 (see section on Meat, Milk, Poultry, and Eggs), the maximum expected residue levels in cow liver and kidney would be about 0.03 ppm and 0.10 ppm, respectively. Therefore, provided the registrant's responses to the points addressed in the section on Metabolism in Animals do not change the proposed tolerance expression (parent and metabolites, determined as 3-chlorosulfonamide acid, and expressed as parent equivalents), the registrant will need to add the following commodities and tolerance levels to a proposed new Section F:

Cattle, mbyp	0.1 ppm
Goats, mbyp	0.1 ppm
Hogs, mbyp	0.1 ppm
Horses, mbyp	0.1 ppm
Sheep, mbyp	0.1 ppm

11b. The registrant is reminded that if the maximum residues in corn grain, or another future poultry feed item that may be treated with MON 12000, exceed 0.1 ppm, a poultry feeding study will be required.

12. No Codex, Canadian, or Mexican tolerances are established for MON 12000. No compatibility problem exists between the proposed U.S. and Codex tolerances.

Recommendations

Until the deficiencies outlined in Conclusions 2, 3a, 3b, 5b, 6d, 8a, 10e, and 11a are satisfactorily resolved, CBTS cannot recommend in favor of the proposed Section 3/permanent tolerance request. Once the results of the requested DRES analysis (see Conclusion 4g) are evaluated, CBTS will issue another memo updating the conclusions/deficiencies listed in this memo.

Note to P.M.:

CBTS defers to RD to determine whether the proposed tank mixes are compatible with the proposed uses and application rates of Banvel®, Beacon®, Accent®, Buctril®, Roundup®, Battalion®, Micro-

Tech®, Partner®, Dual®, Eradicane®, Sutan®, Frontier®, and 2,4-D on field corn and/or grain sorghum.

[redacted]

CBTS recommends that the petitioner be given a copy of this complete review.

Detailed Considerations

Product Chemistry

The review of the product chemistry data submitted with this petition was performed by Dynamac and has undergone secondary review in CBTS [see Attachment II and Attachment III (confidential appendix containing CBI)]. The product chemistry review accurately reflects EPA data requirements and policy. The submitted product chemistry data are not sufficient to fulfill the requirements for this Section 3/permanent tolerance request. As outlined in Attachments I and II, additional data are required to satisfy 61-1, 61-2, 62-1, and 62-2.

Proposed Use

Permit®

Permit® is a water soluble granule formulation containing 75% active ingredient (MON 12000). Permit® is marketed both with a water soluble packaging (as MON 12042 containing 0.69 oz.form./bag) and without a water soluble packaging (as MON 12037) for postemergence use in field corn and grain sorghum.

Field Corn

Permit® can be applied postemergence to field corn from the 2-leaf through layby stage (before the corn is 20 to 30 inches tall). For control of velvetleaf, cocklebur, and other broadleaf weeds in field corn, make 1 or 2 applications of Permit® at the rate of ⅓ to 1⅓ oz.(by weight) of product (0.016 to 0.0625 lb.ai.) per acre per application depending on the type and stage of growth of the weed. Do not exceed 2⅔ oz.(by weight) of product (0.125 lb.ai.) per acre per use season. Mix with a sufficient volume of spray carrier (10 gallon minimum) and a nonionic surfactant (0.25 to 0.5% by volume) or crop oil concentrate (1% petroleum based crop oil concentrate by volume), and apply using ground equipment only. The label also allows the use of fluid nitrogen fertilizers (4% by volume), Accent™, Banvel™, Beacon™, Buctril™, Roundup®, and 2,4-D in tank mixes of Permit®. Following application to corn foliage, allow 30

//

days before grazing livestock, harvesting forage, or harvesting silage.

Grain Sorghum

Permit® can be applied postemergence to grain sorghum from the 2-leaf through layby stage (before grain head emergence). For control of velvetleaf, cocklebur, and other broadleaf weeds in grain sorghum, Permit® may be applied only 1 time at up to ⅔ oz. (by weight) of product (0.032 lb.ai.) per acre per use season. Mix with a sufficient volume of spray carrier (10 gallon minimum) and a nonionic surfactant (0.25 to 0.5% by volume) or crop oil concentrate (1% petroleum based crop oil concentrate by volume), and apply using ground equipment only. The label also allows the use of fluid nitrogen fertilizers (4% by volume), Accent™, Banvel™, Beacon™, Buctril™, Roundup®, and 2,4-D in tank mixes of Permit®. Following application to sorghum foliage, allow 30 days before grazing livestock, harvesting forage, or harvesting silage.

Both

The Permit® label provides the following rotational crop plantback intervals:

crop	replant interval (months)
oats	4
winter wheat	2
spring wheat	4
alfalfa	2
field pea	9
field bean	9
pop corn	1
pumpkin	9
snap bean	9
soybean	1
sweet corn	1
tomato	9
sugar beet	18
sunflower	18

All other crops require a successful field bioassay. Refer to individual product labels to determine rotational crop restrictions when tank mixes are used.

Battalion

Battalion® is a water dispersable granule formulation (MON 12041) containing 15% active ingredient (MON 12000) marketed for preemergence use on field corn only.

Battalion® is formulated to be used preemergence (or early preplant surface-applied or preplant incorporated) on field corn. For control of velvetleaf, cocklebur, and other broadleaf weeds in

field corn, Battalion® may be ground-applied only 1 time at 7 to 10 oz.(by weight) of product (0.065 to 0.094 lb.ai.) per acre, depending on the type and stage of growth of the weed. Do not exceed 10 oz. of Battalion® (0.094 lb.ai.) per acre per use season. Following a soil application of Battalion®, a single postemergence application of Permit® may be made at the recommended rate (0.016 to 0.0625 lb.ai.). For this sequential program, **the combined maximum rate per season of MON 12000 products should not exceed 0.157 lb.ai./A.** The label also allows the use of 2,4-D, Banvel™, Bladex™, Dual™, Eradicane™, Frontier™, Micro-Tech®, Partner®, Roundup®, Sutan™, and 2,4-D in tank mixes of Battalion®.

The Battalion® label provides the following rotational crop plantback intervals:

crop	replant interval (months)
oats	4
winter wheat	4
spring wheat	4
alfalfa	2
field pea	12
pop corn	1
pumpkin	12
snap bean	12
sorghum	1
soybean	1
sweet corn	1
tomato	12
sugar beet	18
sunflower	18

All other crops require a successful field bioassay. Refer to individual product labels to determine rotational crop restrictions when tank mixes are used.

Comments

CBTS defers to RD to determine whether the proposed tank mixes are compatible with the proposed uses and application rates of Banvel®, Beacon®, Accent®, Buctril®, Roundup®, Battalion®, Micro-Tech®, Partner®, Dual®, Eradicane®, Sutan®, Frontier®, and 2,4-D on field corn and/or grain sorghum.

The proposed Permit® label lists various rates of product to use based on weed species and size. These rates were apparently intended to be used on field corn only, since they exceed the maximum proposed label rate for milo by 2X. Monsanto should move this section of the label to immediately follow the field corn directions (and precede the milo directions).

Until the issue of the toxicity of the MON 12000 pyrazole moiety (i.e. 3-chlorosulfonamide acid) is resolved (see sections on Metabolism in Plants and Rotational Crops), the number of

13

rotational crops allowed on the label, as well as the plantback intervals for these crops will need to be restricted (see section on Rotational Crops). As noted in the section on Rotational Crops, Monsanto agreed that, until the TOX studies are completed, they will be happy to have target crop tolerances with an expiration date on corn and milo, and rotational crop tolerances on soybean and wheat only. **Provided that the requested DRES analysis indicates that CBTS can recommend in favor of a conditional registration (see section on Rotational Crops)**, the tolerances, with an expiration date, for rotational crops would be based on the limited field trials (3 sites per crop). Therefore, Monsanto will need to revise their proposed labels for Permit® and Battalion® by deleting the current language concerning rotational crops and add the following:

> Permit® or Battalion® treated milo or field corn fields may be rotated or replanted to milo, field corn, soybeans, or wheat (spring or winter) only. Do not replant or rotate to soybeans or wheat within 12 months of an application of Permit® or Battalion®. Corn or milo can be replanted in the same growing season provided the maximum rate of Permit® and/or Battalion® per season is not exceeded.

Otherwise, crop rotation/replanting to any crop other than corn and milo will need to be restricted.

Nature of the Residue

Metabolism in Plants

A nature of the residue in corn study (MRID# 421394-05) was submitted and reviewed in conjunction with PP#2G4073 (see reviews of G.J. Herndon dated 7/30/92 and 9/8/92). In those reviews CBTS concluded that the nature of the residue in corn was adequately elucidated for both the EUP/temporary tolerance petition being reviewed and any future, Section 3/permanent tolerance request on corn.

In the memo of 7/30/92, CBTS concluded that the metabolism of MON 12000 in corn depends on the mode of application. In postemergence, foliar use, little metabolism and translocation took place; over 86% of the applied herbicide was accounted for as surface residues. This is also shown in the very low residues found in grain; less than 0.3% of the TRR in mature corn plants was detected in the grain fraction. In all corn commodities except grain, over 87% of the detected residues from postemergence applications were identified as unmetabolized parent compound (in grain, 3-chlorosulfonamide acid (3-CSA) was the major metabolite, which was also the major metabolite detected in all commodities treated by preemergence applications of MON 12000 - see below). Where metabolism occurred, the predominant metabolic route appears to be conversion of MON 12000 to chlorosulfonamide acid, by either

14

hydrolysis of the sulfonylurea linkage (3-chlorosulfonamide ester intermediate) or initial ester cleavage (MON 12000 acid intermediate).

In preemergence, soil application, the metabolism of MON 12000 is much more extensive, and appears to begin in the soil, where the sulfonylurea linkage is split. In soil, MON 12000 appears to degrade to 3-chlorosulfonamide ester and aminopyrimidine. The petitioner cited a study which showed that aminopyrimidine is degraded to polar products and CO_2 in soil, which would explain why the pyrimidine ring of MON 12000 did not produce any significant residue levels in corn. Once taken up in the corn plant, the 3-chlorosulfonamide ester is further metabolized into various products, predominantly 3-chlorosulfonamide acid (through cleavage of the methyl ester), with lesser quantities of N-conjugate chlorosulfonamide ester, hydroxymethyl chlorosulfonamide acid, and N-demethylchlorosulfonamide acid.

Comments

The analytical method (see section on Analytical Method) quantitates the pyrazole moiety of MON 12000 (after cleavage, if necessary) and therefore would provide residue levels for either mode of application. Based on the plant metabolism data provided for both pre and postemergence use on corn, the temporary tolerances for field corn and related commodities were established for residues of MON 12000 and its metabolites determined as the 3-chlorosulfonamide acid (3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylic acid) and expressed as parent (MON 12000) equivalents.

Since that time, Monsanto has proposed to change the tolerance expression to include only the parent compound ("exempt" 3-CSA from the requirements of a tolerance) in order to avoid rotational crop tolerances (see section on Rotational Crops).

The issue was presented to the HED Metabolism Committee on 9/15/93. In that meeting, the committee concentrated on the results of the corn metabolism studies, the rat metabolism studies, and the rotational crop studies. The major pyrazole moiety metabolites of MON 12000 that were found in the corn metabolism study, 3-chlorosulfonamide acid and 3-chlorosulfonamide ester, were <u>not</u> found in the rat metabolism study.

As a result of the 9/15/93 meeting (see memo of G.J. Herndon dated 9/28/93), the Metabolism Committee decided that, due to the lack of toxicology data on the 3-CSA and 3-CSE metabolites, coupled with the fact that the results of both the field and confined rotational crop studies indicate that metabolites containing the pyrazole moiety may accumulate in harvested crops planted at an interval greater than one year, they would postpone making a decision on which residue(s) should be regulated from the use of

MON 12000 on corn pending the results of additional toxicology testing (90 day, developmental, and mutagenicity studies) using 3-chlorosulfonamide acid as the dosing material. Once the additional toxicology data are submitted and reviewed, another meeting of the HED Metabolism Committee will probably be necessary to address the question of which residue(s) to regulate. If the metabolite is of comparable or greater toxicity than the parent, it will need to be included in the tolerance for target and rotational crops.

In a meeting held on 11/19/93 (see memo of G.J. Herndon dated 11/22/93), Monsanto explained that they are willing to perform the 3 requested toxicology studies on the metabolite, but would like the Agency to grant them a conditional registration while the studies were being conducted and reviewed. Until the studies are completed, Monsanto would like to have target crop tolerances with an expiration date on corn and milo, and rotational crop tolerances on soybean and wheat. Based on this, HED explained that we would need to make a DRES run to determine the % of the RfD that would be used assuming 100% crop treated and total residue (MON 12000 plus metabolites) for these 4 crops. If the results indicate acceptable risk, HED might be able to recommend in favor of a conditional registration with tolerances having an expiration date. The tolerances for rotational crops would be based on the limited field trials (3 sites per crop).

In a memo from G.J. Herndon dated 11/24/93, CBTS requested a DRES analysis to determine the dietary risks associated with issuing a conditional registration and tolerances with expiration dates for use of MON 12000 on field corn and grain sorghum. The results from the DRES analysis are not yet available, and therefore no conclusions concerning the potential for a conditional registration can be drawn until the analysis is completed. A separate memo will follow.

Metabolism in Animals

Goat (MRID# 421394-06, 425384-01) and hen (MRID# 421394-07, 423962-02, 425384-02) metabolism studies were submitted and reviewed in conjunction with PP#2G4073 (see reviews of G.J. Herndon dated 7/30/92, 11/12/92, 1/21/93). The studies were found to be acceptable for the purposes of the EUP and temporary tolerance request in PP#2G4073, where the regulation of animal commodities was not necessary.

Goat

As noted in the 7/30/92 memo of G.J. Herndon, in the tissues and milk of goats, the major extractable residue was the unmetabolized parent compound. Acid hydrolysis of the initially non-extractable residue yielded aminopyrimidine and 3-chlorosulfonamide acid, indicating the presence of bound or conjugated residues of these two products, MON 12000, and/or 3-

chlorosulfonamide ester.

Based on the results of the lactating cattle feeding study that was submitted as requested (see section on Meat, Milk, Poultry, and Eggs), the regulation of cattle, goats, hogs, horses, and sheep meat by-products is required for the current Section 3/permanent tolerance request. Therefore, as outlined in the 11/12/92 memo of G.J. Herndon (review of a hen metabolism study), Monsanto was requested to address the following points before any future tolerances on livestock commodities were considered:

1. In the HPLC analysis of the double-labeled hen metabolites, the registrant implies that the method is not able to separate or distinguish between aminopyrimidine and 4,6-dihydroxy MON 12000. The registrant is asked to comment on this, as well as how this might impact the goat metabolism study (MRID# 421394-06), since the results from this study do not indicate a potential coelution problem between aminopyrimidine and 4,6-dihydroxy MON 12000.

2. The registrant is asked to explain why the ratios of aminopyrimidine and 3-chlorosulfonamide ester vary in the goat and hen metabolism studies, when both apparently involve spiking MON 12000 onto blank liver samples. Shouldn't the ratios of aminopyrimidine to 3-chlorosulfonamide ester be about 1:1 in the hen study, similar to the results of the goat study?

Poultry

Based on the low residues of MON 12000 on corn grain and the low transfer of residues in the metabolism study, tolerances on poultry products are not required for this Section 3/permanent tolerance request for use of MON 12000 on corn and grain sorghum. However, if additional or different uses of MON 12000 result in the maximum residues in corn grain or another poultry feed item treated with MON 12000 to exceed 0.1 ppm, regulating poultry commodities may be necessary. In this case, CBTS will require additional characterization and identification of MON 12000 metabolites in the previously reviewed laying hen metabolism study (MRID#s 421394-07 and 423962-02). The additional requirements are outlined in Conclusions 5b, 5c, 5d, 5f, 5g, 5h in the memo of G.J. Herndon dated 11/12/92.

Analytical Method

The registrant submitted a proposed analytical method for analysis of MON 12000 residues in field corn RACs that was reviewed in conjunction with PP#2G4073 (see reviews of G.J. Herndon dated 7/30/92, 11/12/92, 12/9/92, 1/21/93, 2/4/93, 3/11/93, 3/16/93, 3/17/93, 7/1/93, and 10/7/93).

"Analytical Method for the Determination of MON 12000 and MON 12000 Metabolites in Field Corn Matrices", Martha A. Schlicher, 10/91, Doc.# RES-012-91
(MRID# 421394-08, vol 1)

RES-012-91 can be used to quantitate residues of MON 12000, MON 12000 acid, 3-chlorosulfonamide ester, and 3-chlorosulfonamide acid residues. The method cleaves any MON 12000 and MON 12000 acid residues to residues of chlorosulfonamide acid and animopyrimidine. Since no aminopyrimidine residues have been found in field corn matrices, any animopyrimidine concentrations found correspond directly to the initial MON 12000 and MON 12000 acid concentrations. The amount of free 3-chlorosulfonamide acid and 3-chlorosulfonamide ester found in the samples is quantitated by subtracting the portion of the 3-chlorosulfonamide acid arising from the MON 12000/MON 12000 acid hydrolysis from the total 3-chlorosulfonamide acid residue obtained (The portion of 3-chlorosulfonamide acid arising from hydrolysis corresponds to the amount of aminopyrimidine found). These residues can be interconverted based on the following molecular weights:

MON 12000 : 434.8
Chlorosulfonamide acid : 239.6
Pyrimidine : 155.2

The method underwent validation, independent lab validation, and Beltsville lab validation for field corn RACs. CBTS and the Beltsville lab concluded that RES-012-91 is adequate for enforcement. The methods used to analyze the processed corn fractions (RES-043-92), milo RACs (RES-012-91, version 2 and RES-026-92) and processed milo commodities (RES-045-92) are essentially the same as the RES-012-91.

The results of the FDA multiresidue method testing of MON 12000 and 3-CSA (MRID# 426614-05) have been sent to FDA and Beltsville (memo of G.J. Herndon dated 10/7/93). Neither MON 12000 nor 3-CSA were sucessfully recovered through Protocols A through E.

Based on the results of the lactating cattle feeding study that was submitted as requested (see section on Meat, Milk, Poultry, and Eggs), the regulation of cattle, goats, hogs, horses, and sheep meat by-products is required for the current Section 3/permanent tolerance request. Therefore, the registrant will need to submit a method for analyzing these meat by-products and the results from both lab and independent lab validation. The method will then be forwarded to the Beltsville lab for their validation. The meat by-products method must be validated by Beltsville before CBTS can recommend in favor of a Section 3/permanent tolerance request for use of MON 12000 on corn and milo.

18

Residue Data

Storage Stability

Corn

Interim storage stability data were provided in MRID# 425384-04 in support of the EUP/temporary tolerance request (see memo of G.J. Herndon dated 1/21/93)

In the current submission, the registrant has provided the following final storage stability study:

> "Storage Stability of MON 12000 and MON 12000 Metabolites in Field Corn Matrices", M.A. Schlicher, 12/93, Monsanto Report# MSL-13129 (MRID# 430426-02).

The sample materials used in the storage stability tests were taken from the representative field corn crop matrices used in the magnitude of the residue study. Three sets each of control forage, fodder, silage, and grain samples were fortified with either 0.10 ppm of MON 12000 or 0.10 ppm of MON 12000 and 0.18 ppm of chlorosulfonamide acid as MON 12000 equivalents. Individual aliquots of each matrix were weighed and stored frozen (<0°F) until fortification at which time the replicate samples for the time point were thawed, fortified, and returned to frozen storage. The results of the analyses are shown in Tables 1 and 2.

Table 1

Frozen Storage Stability of MON 12000 in Corn Products

	% Recovery of Aminopyrimidine in Various Corn Products from 0.10 ppm fortification of MON 12000 and expressed as MON 12000 equivalents			
months in storage (approximate)	forage	fodder	silage	grain
0	86	91	63	84
4	97	82	76	87
6	103	101	74	104
9	108	-	72	92
12	91	87	100	-
15	98	107	-	96
19	133	112	103	138
23	128	85	65	128
25	92	78	64	85
27	87	109	50	83

Table 2

Frozen Storage Stability of Chlorosulfonamide Acid in Corn Products

	% Recovery of 3-Chlorosulfonamide Acid in Various Corn Products from Fortifications of MON 12000 and Chlorosulfonamide Acid (0.28 ppm total) and expressed as MON 12000 equivalents			
months in storage (approximate)	forage	fodder	silage	grain
0	90	65	64	77
4	69	64	65	84
6	90	65	79	-
9	86	66	73	76
12	73	69	76	90
15	51	76	88	83
19	95	70	69	96
23	95	73	-	94
25	86	60	65	76
27	50	60	62	76

The storage stability samples were analyzed by the same method (RES-012-91) that was used to analyze the field samples in the magnitude of the residue study. The Day 0 recoveries are equivalent to method recoveries.

Based on how the method hydrolyzes MON 12000 to aminopyrimidine (the volatile hydrolysis product) and chlorosulfonamide acid (the non-volatile product), recoveries of aminopyrimidine residues reflect the stability of MON 12000. Chlorosulfonamide acid residues correspond to the total residues in the matrices resulting from both MON 12000 hydrolysis and chlorosulfonamide acid residues themselves.

Milo

The sample materials used in the storage stability tests were taken from the representative milo matrices used in the magnitude of the residue study. Sets of control milo hay, silage, and grain samples were fortified with either 0.25 ppm of MON 12000 or 0.091 ppm of chlorosulfonamide acid as MON 12000 equivalents. Individual aliquots of each matrix were weighed and stored frozen (-23 to -27°F) until fortification at which time the replicate samples for the time point were thawed, fortified, and returned to frozen storage. The results of the analyses are shown in Tables 3 and 4.

Table 3

Frozen Storage Stability of MON 12000 in Milo Products

	% Recovery of Aminopyrimidine in Various Milo Products from 0.25 ppm fortification of MON 12000 and expressed as MON 12000 equivalents		
months in storage (approximate)	hay	silage	grain
0	62	86	96
6	100	86	74

Table 4

Frozen Storage Stability of Chlorosulfonamide Acid in Milo Products

	% Recovery of 3-Chlorosulfonamide Acid in Various Milo Products from Fortifications of MON 12000 (0.25 ppm fortifications) and Chlorosulfonamide Acid (0.091 ppm fortifications) and expressed as MON 12000 equivalents		
months in storage (approximate)	hay	silage	grain
0	68	105	84
6	81	82	87

Comments

The available storage stability data are adequate to show that residues of **3-CSA** are stable in field corn RACs for up to 27 months. This covers the time period that the field corn residue samples used in support of this petition were stored (up to 20 months).

The 6 month storage stability period for milo would normally not be sufficient to cover the maximum 10 month period that the field residue samples used in support of this petition were stored. However, since milo and corn are closely related (they are in the same crop group) and 3-CSA has been shown to be stable in field corn RACs at intervals up to 27 months, this will not be a deficiency. The available storage stability data are adequate to show that residues of 3-CSA are stable over the time period that the milo field residue samples used in support of this petition were stored.

The results from the aminopyrimidine recoveries indicate much more variability and less stability than the 3-CSA residues over the same time period. If the need for analyzing aminopyrimidine

arises, the variability in the storage stability recoveries will need to be reexamined.

Magnitude of the Residue

Corn

The registrant conducted residue trials at 20 sites in 17 states in 1990, using both preemergence and postemergence applications. These 17 states are representative of the diversity of growing areas for corn and account for 91 % of the U.S. corn grain and seed production[1]. These data were previous provided in support of 000524-EUP-TO/PP#2G4073 and 000524-EUP-TA (see memos of G.J. Herndon dated 7/30/92 and 11/12/92). The field trials were conducted at rates roughly equivalent to 1 to 1.6X the proposed label rate. The composite of all the corn field trial data was provided in MRID# 423963-03, an overview of which is presented in Tables 5 through 8.

Table 5

Maximum **Corn Grain** Residues for Each Application Mode

	Use Rate (lb.ai./A.)			
Application Mode (# applications)	first	last	total	Maximum Residue (ppm)▲
preemergence (1)	0.13	NA	0.13	0.031
preplant incorporated (1)	0.13	NA	0.13	0.036
early postemergence (1)	0.13	NA	0.13	0.031
postemergence (1)	0.09	NA	0.09	0.039
late postemergence (1)	0.09	NA	0.09	0.029
preemergence + postemergence (2)	0.125	0.125	0.25	0.074
preplant incorporated + late postemergence (2)	0.125	0.125	0.25	0.034
postemergence + late postemergence (2)	0.095	0.095	0.19	0.078

★(from last application)
▲ (total CSA, expressed as parent, and corrected for recovery)
NA : not applicable

[1] Census of Agriculture, 1987, vol. 1, part 51, "United States Summary and State Data", table 24.

23

Table 6

Maximum Corn Fodder Residues for Each Application Mode

Application Mode (# applications)	Use Rate (lb.ai./A.) first	last	total	Maximum Residue (ppm)▲
preemergence (1)	0.13	NA	0.13	0.18
preplant incorporated (1)	0.13	NA	0.13	0.041
early postemergence (1)	0.13	NA	0.13	0.27
postemergence (1)	0.09	NA	0.09	0.21
late postemergence (1)	0.09	NA	0.09	0.37
eemergence + postemergence (2)	0.125	0.125	0.25	0.085
preplant incorporated + late postemergence (2)	0.125	0.125	0.25	0.15
postemergence + late postemergence (2)	0.095	0.095	0.19	1.2

★(from last application)
▲ (total CSA, expressed as parent, and corrected for recovery)
NA : not applicable

Table 7

Maximum Corn Forage Residues for Each Application Mode

pplication Mode (# applications)	Use Rate (lb.ai./A.) first	last	total	Maximum Residue (ppm)▲
preemergence (1)	0.13	NA	0.13	0.019
preplant incorporated (1)	0.13	NA	0.13	0.030
early postemergence (1)	0.13	NA	0.13	0.035
postemergence (1)	0.09	NA	0.09	0.12
late postemergence (1)	0.09	NA	0.09	0.25
preemergence + postemergence (2)	0.125	0.125	0.25	0.056
preplant incorporated + late postemergence (2)	0.125	0.125	0.25	0.070
postemergence + late postemergence (2)	0.095	0.095	0.19	0.29

★(from last application)
▲ (total CSA, expressed as parent, and corrected for recovery)
NA : not applicable

20

Table 8

Maximum Corn Silage Residues for Each Application Mode

Application Mode (# applications)	Use Rate (lb.ai./A.)			Maximum Residue (ppm)▲
	first	last	total	
preemergence (1)	0.13	NA	0.13	0.033
preplant incorporated (1)	0.13	NA	0.13	0.017
early postemergence (1)	0.13	NA	0.13	0.052
postemergence (1)	0.09	NA	0.09	0.074
late postemergence (1)	0.09	NA	0.09	0.15
eemergence + postemergence (2)	0.125	0.125	0.25	0.12
preplant incorporated + late postemergence (2)	0.125	0.125	0.25	0.071
postemergence + late postemergence (2)	0.095	0.095	0.19	0.26

★(from last application)
▲ (total CSA, expressed as parent, and corrected for recovery)
NA : not applicable

Milo

The registrant conducted residue trials at 12 sites in 8 states in 1992, using postemergence applications. These 8 states account for 93% of the U.S. grain sorghum production[2]. A single application of MON-12037 (a 75% active ingredient water dispersable granule formulation) was ground applied to plots 8 to 12 inch tall milo. The spray volume varied from about 10.7 to 20.1 gal./A.; most of the applications were at about 17 gal./A. Applications were made at rates varying from 0.055 lb.ai/A. (1.7X the proposed label rate) to 0.099 lb.ai/A. (3.1X the proposed label rate). In addition, two trial sites received rates of up to 0.38 lb.ai/A. (11.9X the proposed label rate) to be used in a processing study. Samples were analyzed by EN-CAS Analytical Laboratories, Inc. in Winston-Salem, NC using Methods RES-012-91, Version 2 and RES-026-92. The results are presented in Table 9.

[2] Census of Agriculture, 1987, vol. 1, part 51, "United States Summary and State Data", table 24.

25

Table 9

Maximum Residues for Various Milo Commodities

Commodity	Use Rate (lb.ai./A./season)	Site	PHI	Maximum Residue▲
forage	0.063	Washington County, MS	36	0.041
	0.092	Washington County, MS	36	0.085
hay	0.063	Washington County, MS	40	0.176
	0.092	Washington County, MS	40	0.293
silage	0.066	Caddo County, OK	66	0.069
	0.092	Caddo County, OK	66	0.135
grain	0.055	Crittendon County, AR	79	0.081
	0.092	Washington County, MS	78	0.041
stover	0.066	Caddo County, OK	89	0.084
	0.092	Washington County, MS	78	0.101

▲ (total CSA, expressed as parent, and corrected for recovery), uncorrected for method recoveries???

no grain harvested from SD

Comments

Based on the best correlation between the worst case proposed use (maximum rate and shortest PHI) and the field trial data (all the milo data were generated using higher rates than the proposed label rate), the registrant will need to propose a new Section F, that reads as follows:

> Monsanto requests that permanent tolerances be established for the residues of methyl 5-{[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonylaminosulfonyl}-3-chloro-1-methyl-1-H-pyrazole-4-carboxylate and its metabolites determined as 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylic acid and expressed as parent equivalents, in/on the following raw agricultural commodities:
>
> Corn, field
> grain 0.1 ppm
> forage 0.3 ppm
> fodder 1.5 ppm

36

Sorghum, grain	
grain	0.1 ppm
forage	0.1 ppm
fodder/stover	0.1 ppm

Note: Tolerances for sorghum silage and hay are no longer necessary. The commodities will be deleted in the forthcoming revised Table II. Silage residues will be covered by the tolerance on forage.

As noted in the sections on Rotational Crops and Meat, Milk, Poultry, and Eggs, the registrant will also need to propose rotational crop and meat by-product tolerances.

Processing

Corn

A field corn processing study was previously submitted (MRID# 425384-03) and reviewed in a memo of G.J. Herndon dated 1/21/93. CBTS concluded that a tolerance of 0.1 ppm on field corn grain should be adequate to cover the residues on the processed corn commodities listed in Table II of Subdivision O as a result of the proposed use.

Milo

Monsanto submitted the following sorghum grain processing study:

"Residues of MON-12037 in Milo Raw Agricultural Commodities and Processed Milo Fractions", D. Dusek, 1/7/93, Project# AA920020.KS1 (MRID# 430426-01)

The processing study was conducted using sorghum grain grown in Kansas and Texas. Samples were generated from the application of 0.369 or 0.382 lb.ai./A. (about 11.5X the proposed maximum label rate). The grain sorghum samples were harvested and shipped frozen to the Engineering Biosciences Research Center at Texas A&M University (formerly the Food Protein Research and Development Center). Small scale dry-milling procedures were used to produce fractions that were essentially representative of industrial practices. The dry-milling process gave grits, flour, bran, and grain dust. The individual fractions were frozen and returned to Monsanto for analysis. The samples were analyzed by Method RES-045-92, which is essentially the same as the other corn and milo methods proposed for enforcement. Method recoveries averaged 87.5% (grain), 72.2% (grits), 66.8% (flour), 69.7% (bran), and 68.0% (grain dust). The results are shown in Tables 10 and 11.

Table 10

Total Residues of MON 12000 in Processed Sorghum Grain Fractions

	Residues (ppm) at Two Sites Analyzed as Chlorosulfonamide Acid and Expressed As MON 12000 Equivalents*	
grain sorghum matrix	Kansas	Texas
grain (RAC)	0.142	0.075
grits	0.146	0.031
flour	0.065	0.023
bran	0.971	0.393
grain dust	0.371	0.562

* - Results corrected for method recoveries

Table 11

Concentration Factors for Total Residues of MON 12000 in Processed Grain Sorghum Fractions

	Site		
grain sorghum fraction	Kansas	Texas	Average
grits	1.03	0.413	0.72
flour	0.458	0.307	0.38
bran	6.83	5.24	6.0
grain dust	2.61	7.49	5.1

Comments

The results indicate that residues concentrate in the bran and grain dust fractions. Based on a conversation with B. Schneider on 1/28/94 (plant physiologist, HED, CBTS), the older sorghum varieties have a growing season up to 180 days, with the newer hybrids maturing in as little as 90 days from sowing). Even with the new, short-season hybrids, the minimum time between the layby stage (which is the latest that the Permit® proposed label allows MON 12000 to be applied) would be at least 60 days. Based on the proposed early-season use of this herbicide (use would occur before grain head formation) and therefore the low likelihood of the grain exhibiting **primarily** surface residues, as noted in the Phase 3 Technical Guidance for Subdivision O, proposing a separate tolerance on grain dust will not be necessary.

The results of Table 11 indicate that residues of MON 12000 in milo can concentrate by 5.24X when the raw milo is processed into bran. However, based on the soon to be released update of Table II, we no longer consider bran to be a processed commodity of grain sorghum. Therefore, proposing a separate tolerance on bran will not be necessary.

In both cases, a tolerance of 0.1 ppm on milo grain should be adequate to cover the residues on the regulated processed milo commodities as a result of the proposed use.

Rotational Crops

Rotational crop studies were previously reviewed in the memos of G.J. Herndon dated 3/11/93 (confined) and G.F. Kramer, Ph.D. dated 8/30/93 (limited field). The results of both the field and confined rotational crop studies indicate that metabolites containing the pyrazole moiety may accumulate in harvested crops planted at an interval greater than one year. As noted in G.F. Kramer's review of 8/30/93, if the HED Metabolism Committee determines that MON 12000 metabolites containing the pyrazole moiety need to be regulated, the presence of these residues in all rotational crops studied (except lettuce) indicates that extensive field trials will be required to set tolerances for each crop group for which crop rotation will be permitted.

In their meeting held on 9/15/93, the HED Metabolism Committee concluded that no new rotational crop residue data will be required until the additional TOX data requested are submitted and reviewed (see memo of G.J. Herndon dated 9/28/93). However, in a meeting held on 11/19/93 (see memo of G.J. Herndon dated 11/22/93), Monsanto explained that they would initiate additional field rotational crop studies now, rather than wait until the additional toxicology results are reviewed.

In the 11/19/93 meeting, Monsanto explained that they are willing to perform the 3 requested toxicology studies on the metabolite, but would like the Agency to grant them a conditional registration while the studies were being conducted and reviewed. Until the studies are completed, Monsanto would like to have target crop tolerances with an expiration date on corn and milo, and rotational crop tolerances on soybean and wheat. Based on this, HED explained that we would need to make a DRES run to determine the % of the RfD that would be used assuming 100% crop treated and total residue (MON 12000 plus metabolites) for these 4 crops. If the results indicate acceptable risk, HED might be able to recommend in favor of a conditional registration with tolerances having an expiration date. The tolerances for rotational crops would be based on the limited field trials (3 sites per crop).

In a memo from G.J. Herndon dated 11/24/93, CBTS requested a DRES analysis to determine dietary risks associated with issuing a

conditional registration and tolerances with expiration dates for use of MON 12000 on field corn and grain sorghum. The residue values to be used in the DRES analysis are:

RAC	Maximum Residue (total)
field corn grain	0.1 ppm
sorghum grain	0.02 ppm
soybean seed	0.5 ppm
wheat grain	0.1 ppm

The residue levels for the corn and sorghum would apply to target and rotational crop uses; the soybean and wheat residue levels apply to rotational crop uses only.

The results from the DRES analysis are not yet available, and therefore no conclusions concerning the potential for a conditional registration can be drawn until the analysis is completed. A separate memo will follow. However, if the DRES memo indicates that CBTS can recommend in favor of a conditional registration, the registrant will need to provide a new Section F that reads as follows:

> Monsanto requests that permanent tolerances be established for the indirect or inadvertent residues of methyl 5-{[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonylaminosulfonyl}-3-chloro-1-methyl-1-H-pyrazole-4-carboxylate and its metabolites determined as 3-chloro-1-methyl-5-sulfamoylpyrazole-4-carboxylic acid and expressed as parent equivalents, in/on the following raw agricultural commodities when present therein as a result of the application of halosulfuron to field corn and/or grain sorghum:
>
> | | | |
> |---|---|---|
> | Soybean | | |
> | | seed | 0.5 ppm |
> | | forage | 0.5 ppm |
> | | hay | 0.5 ppm |
> | Wheat | | |
> | | grain | 0.1 ppm |
> | | forage | 0.1 ppm |
> | | straw | 0.2 ppm |

Otherwise, crop rotation/replanting to any crop other than corn and milo will need to be restricted.

Meat, Milk, Poultry, and Eggs

For the purposes of the EUP and temporary tolerance request in PP#2G4073, the regulation of animal commodities was determined not to be necessary (see memo of G.J. Herndon dated 7/30/92). However, as noted in the R. Loranger memo of 10/22/91 (and reiterated in the G.J. Herndon memo of 7/30/92), CBTS concluded that:

a). Due to the higher levels of residues observed in cattle feed items and the fact that the estimation of residues in cattle products involves an extrapolation across species (goat vs. cow), a cow feeding study will need to be submitted prior to a Section 3/permanent tolerance request for use of MON 12000 on corn.

b). Provided that the maximum residues in corn grain and other poultry feed items that may be treated with MON 12000 remain at or below 0.1 ppm, a poultry feeding study will not be required.

Cattle

In response to this, Monsanto submitted the following lactating cattle feeding study:

"MON 12000 Residues in Milk and Edible Tissue of Lactating Dairy Cattle", D.D. Arras and M.A. Schlicher, 11/92, Study MSL 12185 (MRID# 426614-07).

MON 12000 was administered in gelatin capsules to lactating dairy cattle (four animals/dose group) once daily for 28 consecutive days at 3 levels (roughly equivalent to 0.5, 1.5, and 5 ppm in the daily diet on a dry weight basis). Four control animals were given untreated capsules. Milk samples were collected from each a.m. and p.m. milking from Day 1 until the day of sacrifice. Within 12 hours after the last dose of test material, the animals were sacrificed and samples of liver, kidney, fat, and muscle were collected, finely ground, and frozen until analysis. The samples were analyzed either by Method RES-021-92 (milk samples) or Method RES-027-92 (meat matrices). Both methods convert MON 12000, MON 12000 acid, des-methyl MON 12000, and chlorosulfonamide ester to a single chemophore, chlorosulfonamide acid. Prior to sample analysis, the performance of the methods was tested using both unlabeled MON 12000 fortifications as well as the radiolabeled goat milk and liver samples obtained from the carbon-14 goat metabolism study. Adequate storage stability of MON 12000 in the various matrices was shown to cover the storage interval of the samples. No residues were detected in the controls above the 0.01 ppm detection limit. The results are shown in Table 12.

Table 12

Maximum Residues in Dairy Cattle Tissues and Milk

	Maximum Residue (ppm)▲						
Dose (ppm)	Whole Milk	Raw Cream	Raw Skim Milk	Muscle	Fat	Liver	Kidney
0.5	NA	NA	NA	NA	NA	0.01	0.02
1.5	NA	NA	NA	< 0.01	< 0.01	0.04	0.11
5.0	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	0.11	0.24

▲ (total CSA, expressed as MON 12000 equivalents)
NA - not analyzed (if a higher feeding level showed no detectable residues, the lower levels were usually not analyzed)

Using the highest single residue values for each of the four matrices, the maximum dietary residue a dairy cow would be exposed to is shown in Table 13.

Table 13

Maximum Residue Exposure of a Cow based on a Diet of MON 12000 Treated Corn

		Maximum Residue (ppm)		
Matrix	% of Diet	Uncorrected	Corrected for % moisture	Total (ppm)
grain	30	0.10	0.11	0.033
forage	10	0.30	1.2	0.12
silage	50	0.30	1.2	0.60
fodder	10	1.5	1.8	0.18
				0.93 ppm

Chicken

A poultry feeding study was not submitted. Residues were previously estimated using the data from the hen metabolism study (see memo of G.J. Herndon dated 7/30/92). A chicken diet consisting of 100% corn grain and a maximum residue value of 0.080 ppm (taken from the 0.094 lb.ai/A. treatment rate at postemergence and late postemergence) was used. Based on the hen metabolism study in which the highest residue value occurred in the liver at 0.196 ppm (based on feeding 9 ppm of MON 12000 in the diet), a reduction in residues is calculated as 0.196 ÷ 9 or 0.0218. Therefore, the maximum expected residue level in chickens is 0.080 × 0.0218 or 0.0017 ppm, which is below the method detection limit.

Comments

Based on Tables 12 and 13, the maximum expected residue levels in cow liver and kidney would be about 0.03 ppm and 0.10 ppm, respectively. Therefore, provided the registrant's responses to the points addressed in the section on Metabolism in Animals does not change the proposed tolerance expression (parent and metabolites, determined as 3-chlorosulfonamide acid, and expressed as parent equivalents), the registrant will need to add the following commodities and tolerance levels to a proposed new Section F:

Cattle, mbyp	0.1 ppm
Goats, mbyp	0.1 ppm
Hogs, mbyp	0.1 ppm
Horses, mbyp	0.1 ppm
Sheep, mbyp	0.1 ppm

The registrant is reminded that if the maximum residues in corn grain, or another future feed item that may be treated with MON 12000, exceed 0.1 ppm, a poultry feeding study will be required.

Other Considerations

No Codex, Canadian, or Mexican tolerances are established for MON 12000. No compatibility problem exists between the proposed U.S. and Codex tolerances.

Attachment I : Product Chemistry Review of MON 12000 (6 pages)

Attachment II : Confidential Appendix portion of the Product Chemistry Review of MON 12000 (9 pages)

cc (without attachment): circu., E. Haeberer (section head).

cc (with attachments): PP#3F04193, RF, Dynamac, G.J. Herndon.

RDI: Section Head: E. Haeberer: 3/3/94,
Branch Senior Scientist: R.A. Loranger: 3/3/94.
Branch Chief: D. Edwards: 3/3/94.

H7509C: CBTS: G.J. Herndon: 305-6362: CM#2, Rm. 804C: 2/25/94.