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

AUG 16 1993

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**MEMORANDUM**

**SUBJECT:** Mepiquat Chloride. Guideline 171-4(d) Analytical Method for Milk. Reregistration Case No. 2375. Chemical No. 109101. MRID #42546201 and 42546202. DP Barcode D186624. CBRS #11,202.

**FROM:** Steven A. Knizner, Chemist *St. A. Knizner*  
Special Review Section I  
Chemistry Branch II - Reregistration Support  
Health Effects Division (H7509C)

**THRU:** Edward Zager, Chief *E. Zager*  
Chemistry Branch II - Reregistration Support  
Health Effects Division (H7509C)

**TO:** Ruby Whitters, PM Team 52  
Accelerated Reregistration Branch  
Special Review and Reregistration Division (H7508W)

The Mepiquat Chloride Phase 4 Review (S. Funk, 1/15/91) specified residue chemistry data requirements including animal residue analytical methods and an independent laboratory method trial. BASF Corporation (1992; MRIDs 42546201 and -02) has submitted an animal residue analytical method along with recoveries and an independent laboratory validation. These data were reviewed by Acurex Corp. and have undergone secondary review by CBRS to reflect Branch policies.

The available metabolism data indicate that levels of radioactive residues other than parent are present in liver and milk at >10%. If the hydroxy mepiquat metabolites identified in the goat metabolism study are deemed to be of toxicological concern, additional validation data will be required. Additionally, if designated as a regulated metabolite, hydroxylated mepiquat chloride metabolites must be tested through FDA multiresidue protocols C, D, and E. The HED Metabolism Committee will soon meet and decide upon the toxicological significance of the hydroxy metabolites.

The data indicate that BASF method A9104 adequately recovers residues of the parent mepiquat chloride from poultry muscle, liver and eggs, as well as, ruminant muscle, fat,



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liver, kidney, and raw milk. The submitted independent laboratory validation (1992; MRID 42546202) of BASF method A9104 for calf liver and raw milk is adequate. However, as noted above, if the hydroxy mepiquat metabolites identified in the goat metabolism study are deemed to be of toxicological concern, additional validated methods may be required.

The registrant should submit a copy of BASF method A9104, including a statement that the method may not be valid for mepiquat determinations in pasteurized and homogenized milk (i.e., may be valid only for raw milk), for Agency validation.

If you need additional input please advise.

Attachment.

cc: S.F., circ., R.F., List B File, S.Knizner  
H7509C:CBRS:CM#2:305-6903:SAK:sak:Mepiquat.rev:8/12/93

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**MEPIQUAT CHLORIDE**  
**(Chemical Code 109101)**  
**(CBRS No. 11202; DP Barcode D186624)**

**TASK 2B**

**Phase 5-**  
**Reregistration Review**  
**Residue Chemistry**

April 1, 1993

Contract No. 68-DO-0142

Submitted to:

U.S. Environmental Protection Agency  
Arlington, VA 22202

Submitted by:

Acurex Environmental Corporation  
Eastern Regional Operations  
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MEPIQUAT CHLORIDE

(Chemical Code 109101)

(CBRS No. 11202; DP Barcode D186624)

PHASE 5 - REREGISTRATION REVIEW

RESIDUE CHEMISTRY

Task 2B

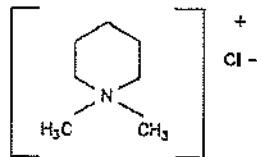
BACKGROUND

The Mepiquat Chloride Phase 4 Review (S. Funk, 1/15/91) specified residue chemistry data requirements including residue analytical methods. Specifically, data collection analytical methods for the determination of the conjugated hydroxylated mepiquat chloride metabolite in milk were required. The Phase 4 Review also indicated that if the hydroxylated mepiquat chloride metabolites are to be regulated, regulatory methods would also be required.

BASF Corporation (1992; MRIDs 42546201 and -02) has submitted a residue analytical method along with recoveries and an independent laboratory validation. These data are reviewed here to determine their adequacy in fulfilling outstanding residue chemistry data requirements. The Conclusions and Recommendations stated below apply only to residue analytical methods.

The qualitative nature of residue of mepiquat chloride in plants is adequately understood. Cotton plant metabolism data (R. Perfetti, CBRS No. 10229, 3/5/93) indicate that the parent compound, mepiquat chloride, is the residue of concern, accounting for >90% of the total radioactive residue in cotton forage and cottonseed. Method I in PAM, Vol. II, is described as very specialized and having recoveries in the 50% range, but is considered adequate for tolerance enforcement purposes. Tolerances for residues of mepiquat chloride are currently expressed in terms of N,N-dimethylpiperidinium chloride (40 CFR §180.384).

There are no established or proposed Codex MRLs for mepiquat chloride. Therefore, no compatibility questions exist with respect to U.S. tolerances and Codex.



Mepiquat chloride

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## CONCLUSIONS

1. BASF residue analytical method A9104 adequately recovers mepiquat chloride from animal commodities. However, if the 4-hydroxy mepiquat metabolites identified in the goat metabolism study are found to be of toxicological concern, additional data will be required.
2. The submitted independent laboratory validation (1992; MRID 42546202) of BASF method A9104 is adequate. However, if the 4-hydroxy mepiquat metabolites identified in the goat metabolism study are deemed to be of toxicological concern, additional validated methods may be required.
3. The registrant should submit a copy of BASF method A9104, including a statement that the method may not be valid for mepiquat determinations in pasteurized and homogenized milk (i.e., may only be valid for raw milk), for Agency validation.

## DETAILED CONSIDERATIONS

### Residue Analytical Methods

BASF Corporation submitted (1992; MRIDs 42546201 and -02) BASF residue analytical method A9104 along with recoveries and an independent laboratory validation. BASF method A9104 and BASF method 286 (reviewed under CBRS No. 10658) are essentially the same method. Recoveries from poultry and ruminant samples fortified with mepiquat chloride are summarized in Table 1 below.

BASF method A9104 involves extraction of residues into water/hydrochloric acid (2M HCl)/acetone (100/1/200; v/v/v) solution by maceration. The extract is filtered, concentrated, and washed with DCM. The pH of the acidic aqueous phase is adjusted to alkaline, residues are partitioned into DCM containing dipicrylamine, then into acidic aqueous solution, concentrated, applied to an alumina column, eluted with acetone/methanol (95/5; v/v), concentrated, and determined by ion chromatography using conductivity detection. The reported detection of limit is 0.05 ppm for mepiquat chloride.

The data indicate that BASF method A9104 adequately recovers residues of the parent mepiquat chloride from poultry muscle, liver and eggs, as well as, ruminant muscle, fat, liver, kidney, and milk. The available metabolism data indicate that levels of radioactive residues other than parent are present in liver and milk at > 10%. If the 4-hydroxymepiquat metabolites identified in the goat metabolism study are deemed to be of toxicological concern, additional validation data will be required.

Table 1. Recoveries of mepiquat chloride from fortified poultry and ruminant tissues by BASF method A9104 (numbers of samples given in parentheses).

Substrate	Fortification Level	Percent Recovery
Poultry: Eggs	Control	< 0.05 ppm (4)
	0.05	70-89 (4)
	1.0	78-85 (4)
Muscle	Control	< 0.05 ppm (2)
	0.05	83, 88
	2.0	89, 87
Liver	Control	< 0.05 ppm (2)
	0.05	91, 90
	5.0	75, 75
Ruminant: (Cow) Milk	Control	< 0.05 ppm (3)
	0.05	85-92 (4)
	0.5	85-88 (4)
Muscle	Control	< 0.05 ppm (2)
	0.05	68, 72
	1.0	83, 69
Fat	Control	< 0.05 ppm (2)
	0.05	82, 68
	0.5	79, 80
Liver	Control	< 0.05 ppm (2)
	0.05	80, 81
	2.0	82, 74
Kidney	Control	< 0.05 ppm (2)
	0.05	74, 70
	5.0	78, 84

The independent laboratory validation of BASF method A9104 conducted by Biospherics was successful on ruminant liver and milk by the third attempted trial. Results are summarized in Table 2 below. One modification was employed for each of the trials. Translucent bottles were substituted for centrifuge tubes in the centrifugation step. This subsequently required that the solution be transferred into a separatory funnel to allow for separation of phases. The first trial incorrectly employed activated alumina that was not acidic. This was corrected for the second trial. The second trial encountered emulsions in milk extracts that were carried through the method as required, but solutions containing emulsions were not centrifuged as specified by the method. The lab reported that low recoveries were a result of

interfering emulsions. Contact with the sponsor revealed that the development of the method had been limited to raw milk, and the pasteurized and homogenized milk that they had been instructed to use had not been investigated. Trials 3 and 4 were successfully completed on liver and raw milk.

The registrant should submit a copy of BASF method A9104, including a statement that the method may not be valid for mepiquat determinations in pasteurized and homogenized milk, for Agency validation. If additional residues are deemed of toxicological concern, additional methods and validation data may be required.

Table 2. Independent laboratory validation of BASF method A9104 by Biospherics Laboratory.

Substrate	Fortification Level	Percent Recovery <sup>a</sup> , (No. of Samples)			
		Trial 1	Trial 2	Trial 3	Trial 4
Calf liver	Control	ND (3)	ND	ND (3)	NP
	0.10	ND- <0.03 ppm (3)	--	90-107 (3)	
	0.5	ND- <0.12 ppm (3)	86, 91	68-101 (3)	
Pasteurized milk	Control	<0.03 ppm (3)	ND	NP	NP
	0.05	SL <sup>c</sup> , <0.03 ppm, 81	--		
	0.25	<0.06 ppm (3)	<0.06 ppm, 31		
Raw milk	Control	NP	NP	ND (2), SL	ND (2), <0.03 ppm
	0.05			77-88 (3)	88-96 (3)
	0.25			60-65 (3)	76-93 (3)

<sup>a</sup>Results are reported as presented by the registrant; ppm values were reported if recovery was significantly less than expected. <sup>b</sup>NP=trial not performed. <sup>c</sup>SL=sample lost during preparation.



References

Citations for the MRID documents referenced in this review are presented below. Submissions reviewed in this document are indicated by shaded type.

42546201: Burkey, J.; Malinsky, D. (1992) Method for Determination of Mepiquat Chloride Residues in Chicken and Cow Matrices Based on Ion Chromatography. Lab Project Number: A9104-92/5130. Unpublished study prepared by BASF Corp. 59 p.

42546202: Gilles, C. (1992) Independent Laboratory Validation of Methodology to Determine Mepiquat Chloride in Animal Matrices. Lab Project Number: B9109-NI. Unpublished study prepared by Biospherics Incorporated. 67 p.

Agency Memoranda

CBRS No.: 10229  
Subject: Response to the Mepiquat Chloride Phase IV Review: Cotton Metabolism  
From: R. Perfetti  
Dated: 3/5/93  
MRID(s): 42330804