FERBAM (DITHIOCARBAMATES, 105)

EXPLANATION

Ferbam was originally evaluated in 1965 (toxicology) and 1967 (toxicology and residues) and is included in the dithiocarbamate group. Ferbam is a broad spectrum fungicide for the control of certain diseases in fruit trees, small fruits and berries, potatoes, ornamentals, conifers and tobacco.

The compound was evaluated at the present Meeting within the CCPR Periodic Review Programme.

IDENTITY

ISO common name: ferbam

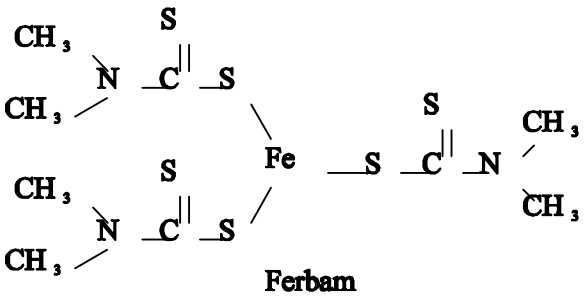
Chemical name

IUPAC: iron tris(dimethyldithiocarbamate)
iron(III) dimethyldithiocarbamate
ferric dimethyldithiocarbamate

CA: (*OC*-6-11)-tris(dimethylcarbamodithioato-*S*,*S*')iron

CAS registry no: 14484-64-1
CIPAC no: 57
EEC no: 238-484-2

Structural formula:



Ferbam

Molecular formula: $C_9H_{18}FeN_3S_6$

Molecular mass: 416.51

Physical and chemical properties

Pure active ingredient

Vapour pressure:	$<1.2\times10^{-4}$ Pa at 25°C (Lemal, 1986a).
Melting point:	>120°C
Octanol/buffer pH 8	
partition coefficient:	log P_{OW} = -1.6 (Lemal, 1986b)
Specific gravity:	0.21 g/cm^3

Lemal (1986a) measured the vapour pressure of ferbam by a gas saturation method. Nitrogen gas was passed through ferbam coated on a support material with a very high surface area and maintained at 25°C, then through a cotton wool dust filter followed by traps containing water. The contents of the absorption traps were analysed for iron by atomic absorption spectrometry. No iron was detected in the traps. The vapour pressure of ferbam at 25°C did not exceed 1.2×10^{-4} Pa.

Lemal (1986b) measured the octanol-water partition coefficient of ferbam (96%) according to OECD Guideline 107 (OECD 1981). Instead of water a pH 8 buffer was used. The octanol and aqueous phases were analysed for Fe using inductively coupled plasma emission spectrometry. The concentration of ferbam in the pH 8 buffer was about 40 times that in the octanol. In a series of tests the values for log P_{OW} ranged from -1.6857 to -1.4582, with a median value of -1.6292 at 20°C.

Technical material

The Meeting was informed that ferbam technical is not produced as such, but the synthesised ferbam is taken through the manufacturing process direct to the formulated product.

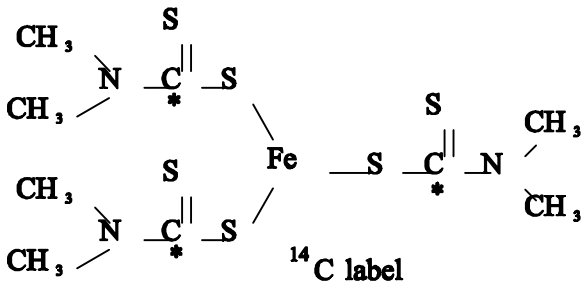
Formulations

Water dispersible granule, 76WG.

METABOLISM AND ENVIRONMENTAL FATE

Animal metabolism

Information was made available to the Meeting on studies of ferbam metabolism in lactating goats and sheep.



Tissue, milk and excreta residues were measured in lactating goats (2 goats, each weighing approximately 45 kg) dosed once daily after the morning milking for 5 consecutive days orally by capsule with 500 mg [*thiocarbonyl*-^{14}C]ferbam at 11.4 and 11.1 mg/kg bw/day, equivalent to 220-250 ppm ferbam in the feed (Daun, 1993). The feed consumption was 1 kg/animal/day of a grain

mixture (shelled maize, oats, mineral mix, wet molasses, dairy pellets) as well as alfalfa grass hay provided *ad libitum*; the mean total daily feed consumption was 2.0-2.3 kg. The animals were hand-milked twice daily; the milk production was 1.5-1.6 kg per day. Milk and excreta were collected throughout, and the goats were slaughtered 6 hours after the final dose for tissue collection.

The distribution of ^{14}C was as shown below.

	^{14}C % of dose	
	Goat 1	Goat 2
Milk	0.70	0.79
Urine	8.3	11.9
Faeces	32.1	25.0
Tissues	2.7	5.6
TOTAL	43.8	43.3

Levels of ^{14}C in the milk increased for the first 2 or 3 days of feeding and then reached a plateau (Table 1). Levels of ^{14}C were higher in the liver than in other tissues (Table 2) and higher in the kidneys than in fat and muscle. Less than 50% of the dose was accounted for by the ^{14}C found in the milk, urine and faeces. It is possible that ^{14}C was lost as $^{14}CS_2$ or $^{14}CO_2$ in expired air, which was not collected.

Most of the ^{14}C residues in the milk, liver, kidneys, muscle and fat were not extractable with a chloroform/methanol/water mixture until after protease treatment. The soluble ^{14}C components produced by protease were mostly polar water-soluble compounds. Lactose and casein containing the ^{14}C label were isolated from the milk. Urea containing ^{14}C was isolated from the urine. This evidence supported other strong indications that much of the ^{14}C in the milk and tissues had been incorporated into natural products.

Table 1. Levels of ^{14}C in milk produced by 2 goats dosed daily with [^{14}C]ferbam equivalent to 220-250 ppm in the feed (Daun, 1993).

Day	^{14}C as ferbam, mg/kg milk			
	Goat 1, am milking	Goat 1, pm milking	Goat 2, am milking	Goat 2, pm milking
1		0.96		0.94
2	1.8	2.3	2.0	2.9
3	2.4	2.8	2.9	3.3
4	2.8	4.0	3.4	3.9
5	2.9	3.4	3.5	3.7

Table 2. Levels of ^{14}C in tissues and fluids from 2 goats dosed daily with [^{14}C]ferbam equivalent to 220-250 ppm in the feed and slaughtered 6 hours after the final dose (Daun, 1993).

Sample	^{14}C as ferbam, mg/kg	
	Goat 1	Goat 2
Bile	6.2	13.2
Blood	2.5	3.2
Fat (omental)	0.47	0.66
Fat (renal)	0.54	0.89
Kidneys	8.3	9.4
Liver	63	75
Muscle	1.5	1.9

Hunt and Gilbert (1976) dosed sheep (ewes) orally by gelatin capsule with [^{3}H]ferbam and [^{35}S]ferbam and examined the excreta and tissues for the radiolabels. One sheep weighing 32 kg was dosed with [^{3}H]ferbam at 0.74 mg/kg bw and [^{35}S]ferbam at 0.45 mg/kg bw, a total dose of 1.19 mg ferbam/kg bw. The second sheep, also weighing 32 kg, was treated with 14.5 mg [^{35}S]ferbam equivalent to 0.45 mg/kg bw. The sheep were slaughtered 72 hours after dosing for tissue collection and analysis.

Over 80% of the dosed ^{3}H but only 23-24% of the ^{35}S was excreted in the urine and faeces (Table 3). This is consistent with studies of thiram in rats which showed that 40-60% of the CS_2 part of the molecule was eliminated as volatile compounds in exhaled air. The level of ^{3}H in the liver was much higher than that of ^{35}S, demonstrating that the dithiocarbamic acid moiety had largely been degraded (Table 4).

Table 3. Excretion of ^{35}S and ^{3}H from 2 sheep dosed with [^{35}S]ferbam + [^{3}H]ferbam (sheep A) and [^{35}S]ferbam (sheep B) and slaughtered 76 hours later (Hunt and Gilbert, 1976).

% of dose					
Sheep A				Sheep B	
Urine		Faeces		Urine	Faeces
^{35}S	^{3}H	^{35}S	^{3}H	^{35}S	^{35}S
12	62	11	20	14	10

Table 4. Residues of ^{35}S and ^{3}H (expressed as ferbam) in tissues of 2 sheep dosed with [^{35}S]ferbam + [^{3}H]ferbam (sheep A) and [^{35}S]ferbam (sheep B) and slaughtered 76 hours later (Hunt and Gilbert, 1976).

Sample	Residues of radiolabel, expressed as ferbam, mg/kg		
	Sheep A		Sheep B
	^{35}S	^{3}H	^{35}S
Fat, omental	0.05	0.09	0.04
Kidneys	0.72	0.81	0.77
Liver	0.66	3.4	1.0
Muscle	0.14	0.22	0.11

Plant metabolism

No information was available.

Environmental fate

No information was available on the fate of ferbam in soils or in water/sediment systems.

METHODS OF RESIDUE ANALYSIS

Analytical methods

The methods for ferbam are the same as those for other dithiocarbamates: acid hydrolysis to release CS_2, which is then measured by head-space gas chromatography.

In the procedure of the Dutch method manual (Ministry of Welfare, Health and Cultural Affairs, The Netherlands, 1988) dithiocarbamates are converted to CS_2 by treatment with hydrochloric acid in the presence of stannous chloride. The CS_2 in the head-space is determined by GLC with either an ECD or FPD in the sulphur mode.

Westberg and Tufts (1990) described the CS_2 evolution head-space GLC procedure used in the ferbam mango trials. The sample was reacted with stannous chloride/hydrochloric acid reagent at 100°C in a sealed reaction flask. An aliquot of the head-space gas was analysed by GLC and compared with ferbam standards similarly reacted and injected. Recoveries were satisfactory at 0.02, 0.3, 0.5 and 7.0 mg ferbam/kg. The LOD was 0.02 mg ferbam/kg. Koch (1996) used a similar method in a study of the frozen storage stability of ferbam and ziram in apples. Satisfactory recoveries were recorded for apples fortified at 0.2 and 6 mg ferbam/kg.

Stability of pesticide residues in stored analytical samples

Koch (1996) tested the stability of ferbam residues in macerated apples fortified at 1 mg/kg and stored in head-space bottles at -20°C for 22 weeks. Samples were analysed as indicated above. Ferbam residues were stable under these storage conditions for the duration of the experiment.

Table 5. Freezer storage stability of ferbam in macerated apples fortified at 1 mg/kg and stored at -20°C (Koch, 1996).

Storage period	Ferbam remaining in stored sample, mg/kg (as ferbam)	Method recovery, %, at time of stored sample analysis
0 day	0.93, 0.94	109, 104
2 weeks	0.79, 0.84	81, 74
4 weeks	0.83, 0.90	76, 84
12 weeks	0.96, 0.90	82, 94
22 weeks	0.78, 0.83	72, 89

Definition of the residue

Ferbam residues are measured as evolved CS_2 by the same methods as are used for the other dithiocarbamates. The samples from the supervised trials on ferbam have been analysed by these methods. The Meeting agreed that ferbam should be included in the definition of the dithiocarbamate residues (*The MRLs refer to total dithiocarbamates, determined as CS_2 evolved during acid digestion and expressed as mg CS_2/kg*) if adequate critical supporting studies become available.

USE PATTERN

Ferbam is a broad-spectrum fungicide for the control of certain diseases in fruit trees, small fruit and berry crops, potatoes, ornamentals, conifers and tobacco. The Meeting was provided with information on registered uses on these crops. The registered uses of ferbam on fruits and potatoes are summarized in Table 6.

Table 6. Registered uses of ferbam on fruits and potatoes. All foliar applications.

Crop	Country	Form	Application			PHI, days
			Max rate per applic., kg ai/ha	Spray conc., kg ai/hl	Number	
Apple	USA	WG	0.86-1.7	0.09-0.18	3-5	7
Cherry	USA	WG	1.3	0.14	2-3	0
Citrus fruit	USA	WG	1.3	0.14	2	0
Cranberry	USA	WG	1.7	0.18	5	stage M28
Grape	USA	WG	1.7	0.18	3	7
Nectarine	USA	WG	1.3	0.14	1-2	21
Peach	USA	WG	1.3	0.14	1-2	21
Pear	USA	WG	1.3	0.14	5	7
Potato	UK	WP	0.17	0.043-0.085	~10	7

M28: 28 days after mid-bloom

RESIDUES RESULTING FROM SUPERVISED TRIALS

Data from supervised trials on mangoes are summarized in Table 7.

Residues, application rates and spray concentrations have generally been rounded to 2 significant figures or, for residues near the LOD, to 1 significant figure. Residues are not corrected for recoveries.

The trials were fully reported and well documented. Ferbam was analysed by a CS_2 evolution method and residues had been expressed as ferbam. All the residues reported in this monograph are expressed as CS_2 irrespective of the original expression. The theoretical factor 0.547 was used to calculate CS_2 values from ferbam values.

Ferbam was applied to two test plots of mangoes by an airblast sprayer. Each test plot comprised 93 trees. Four replicate samples were taken from each plot at each sampling and analysed separately. Samples were stored at -18°C for 3-3½ months after harvest before analysis.

Table 7. Residues of ferbam (as CS_2) in mangoes (Tommy-Atkins variety) from foliar applications of ferbam WG in supervised trials in the USA. The 4 values at each PHI are from 4 replicate samples. Residues are expressed on a whole fruit basis.

Application			PHI, days	Ferbam residues as CS_2, mg/kg	Ref.
kg ai/ha	kg ai/hl	No.			
4.3	0.18	11	0 7 14 21	0.43 0.39 0.13 0.32 0.08 0.17 0.37 0.44 0.17 0.12 0.17 0.11 0.17 0.43 0.07 0.14	UCB 27-FER/91049-11
4.3	0.18	16	0 7 14 21	0.28 0.41 0.44 0.36 0.31 0.10 0.25 0.85 0.14 0.23 0.12 0.26 0.16 0.06 0.25 0.12	UCB 27-FER/91049-16

FATE OF RESIDUES IN STORAGE AND PROCESSING

No information was available.

RESIDUES IN FOOD IN COMMERCE OR AT CONSUMPTION

Monitoring data for dithiocarbamates are included in the monograph on thiram.

NATIONAL MAXIMUM RESIDUE LIMITS

The Meeting was aware that the following national MRLs had been established.

Country	Commodity and MRL, mg/kg
Netherlands	see dithiocarbamates
USA[1]	almonds 0.1; apples 7; apricots 7; asparagus 7; beans 7; beet greens 7; beets 7; blackberries 7; blueberries 7; boysenberries 7; broccoli 7; Brussels sprouts 7; cabbage 7; carrots 7; cauliflower 7; celery 7; cherries 7; citrus fruits 7; collards 7; corn 7; cranberries 7; cucumbers 7; currants 7; dates 7; dewberries 7; egg plants 7; gooseberries 7; grapes 7; guavas 7; kale 7; kohlrabi 7; lettuce 7; loganberries 7; mangos 7; melons 7; mustard greens 7; nectarines 7; onions 7; papayas 7; peaches 7; peanuts 7; pears 7; peas 7; peppers 7; plums 7; pumpkins 7; quinces 7; radish tops 7; radishes 7; raspberries 7; rutabaga tops 7; rutabagas 7; spinach 7; squash 7; strawberries 7; summer squash 7; tomatoes 7; turnip greens 7; turnips 7; youngberries 7.

[1] Residue definition: residues calculated as zinc ethylenebisdithiocarbamate

APPRAISAL

Ferbam was originally evaluated in 1965 (toxicology) and 1967 (toxicology and residues) and is included in the dithiocarbamate group of compounds. The compound was evaluated at the present Meeting within the CCPR Periodic Review Programme.

Ferbam is a broad-spectrum fungicide for the control of certain diseases in fruit trees, small fruits and berries, potatoes, ornamentals, conifers and tobacco.

The Meeting received information on the metabolism of ferbam in goats and sheep, methods of residue analysis, the stability of residues in stored analytical samples, approved use patterns, and supervised residue trials on mangoes.

When two lactating goats were dosed for 5 days with [*thiocarbonyl*-^{14}C]ferbam at a rate equivalent to 220-250 ppm ferbam in the feed, the levels of ^{14}C in the milk increased for the first 2 or 3 days of feeding and then reached a plateau. A large part of the administered ^{14}C was not accounted for (59% and 62%). By analogy with the animal metabolism of thiram losses as CS_2 and CO_2 in expired air would be expected, but ^{14}C in expired air was not measured. More of the ^{14}C dose was in the faeces (25% and 32%) than in the urine (8.3% and 11.9%), tissues (2.7% and 5.6%) or milk (0.70% and 0.79%).

Levels of ^{14}C were much higher in the liver (63 and 75 mg/kg ferbam equivalent) than in the kidneys (8.3 and 9.4 mg/kg), muscle (1.5 and 1.9 mg/kg), or fat (0.47-0.89 mg/kg). Most of the ^{14}C in the milk and tissues was not extractable without protease treatment, which produced polar water-soluble compounds incorporating the ^{14}C. Lactose and casein containing ^{14}C were isolated from the milk.

In a sheep given a single dose of [^{3}H]ferbam + [^{35}S]ferbam and slaughtered 72 hours later for tissue collection more than 80% of the dosed ^{3}H but only 23-24% of the ^{35}S was excreted in the urine and faeces. This is consistent with the animal metabolism of thiram where 40-60% of the CS_2 part of the molecule was eliminated as volatile compounds in exhaled air.

The level of ^{3}H in the liver was much higher than in the other tissues, but the levels of ^{35}S in the liver and kidneys were much the same. The level of ^{3}H in the liver was much higher than that for ^{35}S, demonstrating that the dithiocarbamic acid moiety had largely been degraded.

The analytical methods for ferbam residues are the same as those for other dithiocarbamates. They rely on acid hydrolysis to release CS_2, which may then be measured by head-space gas

chromatography or by spectrophotometry.

The head-space GLC methods used in the supervised trials on mangoes and the frozen storage stability studies on apples gave satisfactory recoveries of ferbam.

Ferbam residues were stable in macerated apples fortified at 1 mg/kg and stored at -20°C for 22 weeks.

Generally, the information on ferbam was quite limited. For a compound in the periodic review programme an adequate set of supporting studies is needed. Because of the absence of plant metabolism and environmental fate studies the Meeting would not have been able to recommend MRLs for dithiocarbamate residues from uses of ferbam even if adequate information on GAP and data from supervised trials had been available for some commodities.

Dithiocarbamate MRLs are derived from supervised trials on specific dithiocarbamate compounds according to the relevant GAP. The table of recommended MRLs for dithiocarbamates indicates the compound or compounds for which data have been evaluated and found to be adequate to support the recommended MRL. Because of the lack of critical supporting studies ferbam is not included in the list of dithiocarbamates with adequate data to support recommended MRLs for dithiocarbamates.

The Meeting recognised that for most dithiocarbamates there are no practical regulatory analytical methods to identify the compound producing dithiocarbamate residues in a food commodity. National governments, under approval and registration systems, may control which uses are permitted.

Ferbam residues found in the supervised trials were measured as evolved CS_2 by the same methods as are used for the other dithiocarbamates. The Meeting agreed that ferbam would be included in the residue definition of the dithiocarbamates if adequate critical supporting studies become available.

The Meeting received data on residues of ferbam from two supervised trials on mangoes in the USA, but the data could not be evaluated because information on GAP for the use of ferbam on mangoes was not available.

Monitoring data for dithiocarbamate residues in commodities in trade are included in the monograph on thiram.

FURTHER WORK OR INFORMATION

Desirable

1. An adequate set of critical supporting studies for ferbam is needed before it can be included in the list of compounds supporting recommended MRLs for dithiocarbamates (see report of 1995 JMPR, Section 2.5.2).

2. Information on attempts to develop specific methods of analysis for ferbam, whether successful or not.

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