13544

033245

Chemical:	**Carbamic acid, ?2-???1-(4-chlorophenyl)-**
PC Code:	**099100**
HED File Code	**21400 MARC**
Memo Date:	**10/09/2001**
File ID:	**DPD278044**
Accession Number:	**412-02-0006**

HED Records Reference Center
12/10/2001

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

October 9, 2001

MEMORANDUM

SUBJECT: PP#0F06139. PC Code 099100. Pyraclostrobin. Outcome of the HED Metabolism Assessment Review Committee (MARC) Meeting Held on September 20, 2001. DP Barcode: D278044.

FROM: Leung Cheng, Chemist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen Dapson, Branch Senior Scientist
Registration Action Branch 3
and
Christine Olinger, Chair
Metabolism Assessment Review Committee
Health Effects Division (7509C)

10/09/2001

TO: Yan Donovan, Executive Secretary
Metabolism Assessment Review Committee
Health Effects Division (7509C)

A. Material Reviewed

Participants at the MARC meeting discussed the metabolism of pyraclostrobin in grape, potato, wheat, goats, hens, rotational crops, water, and rats. Pyraclostrobin is a new fungicide that belongs to the methoxyacrylate class of compounds (D277611, L. Cheng and G. Dannan, Sept-4-2001; EFED handouts prior to and at the meeting).

Plant Metabolism (Target crops)

Results of the metabolism studies in grape, potato and wheat indicate that pyraclostrobin and its desmethoxy metabolite (BF500-3) are the major residues in crop matrices including livestock feeds; tryptophan was found to be the major residue in potato tuber and wheat grain

when carbon-14 was introduced in the tolyl ring (*via* the shikimic acid pathway). The major degradation reactions are the removal of the methoxy group from the carbamate nitrogen and breakage of the ether bond.

Livestock Metabolism

In goats, the major residues are pyraclostrobin and BF500-3 in muscle and fat; parent, BF500-3, and BF500-5 and its sulfate conjugate in milk; parent, BF500-3, and BF500-5 and its sulfate conjugate, and hydroxylated desmethoxy metabolite (500M67) in kidney; and metabolites hydrolyzed to BF500-5 and its hydroxylated compound (BF500-8) in liver.

In poultry, the major residues are pyraclostrobin and BF500-3 in eggs; parent, BF500-3, and hydroxylated BF500-3 (500M64) in fat; the glucuronic acid conjugate of hydroxylated BF500-3 (500M32) in liver. Radioactive residues were below detection in muscle.

The main degradation reactions in livestock consist of demethoxylation, hydroxylation, and conjugation, and breaking of the ether bond.

Analytical Methods

The analytical methods (LC/MS/MS and HPLC/UV) for plant commodities measure pyraclostrobin and its desmethoxy metabolite. The methods (GC/MS and LC/MS/MS) for livestock commodities convert pyraclostrobin and related metabolites to chlorophenylpyrazolol (BF500-5) and hydroxylated chlorophenylpyrazolol (BF500-8) in goats and chlorophenylpyrazolol (BF500-5) and hydroxylated chlorophenylpyrazolol (BF500-9) in poultry.

Rotational Crops

Results of the confined rotational crop studies show that pyraclostrobin and its desmethoxy metabolite are the major residues taken up into the plants.

Water

Pyraclostrobin was determined to be stable to hydrolysis at pH 5, 7, and 9, and is moderately persistent in soil. Several major degradates were found in the various environmental fate studies: BF500-3, BF500-6, and BF500-7.

Rat

The bulk of pyraclostrobin is excreted *via* the urine (11-16%) and feces (85%). A large number of metabolites (nearly 33) were isolated and identified in the urine, feces, and bile. These metabolites indicate that demethoxylation, hydroxylation and cleavage of the ether bond are the major metabolic reactions in rats.

B. Conclusions

The Committee concluded that the plant metabolism studies conducted in the three dissimilar crops are adequate to define the nature of the residue in plants for pyraclostrobin. They also concluded that, in the absence of toxicology data (reflecting direct dosing with the desmethoxy compound) and considering the toxicological effects for risk assessment, the desmethoxy metabolite is assumed to be of similar but not higher toxicity than pyraclostrobin. Also, major metabolites deriving from breakage of the chlorophenylpyrazol and tolyl rings are considered to be significantly less toxic relative to pyraclostrobin.

Tolerances for plants should be established for the combined residues of pyraclostrobin [carbamic acid, [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl] phenyl]methoxy-, methyl ester] and its desmethoxy metabolite [methyl 2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl]phenyl carbamate]. The same two compounds should be assessed for dietary exposure.

Tolerances for livestock should be established for the combined residues of pyraclostrobin and its metabolites convertible to 1-(4-chlorophenyl)-1H-pyrazol-3-ol (BF500-5) and 1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-ol (BF500-8), because the analytical methods quantitate the major metabolites bearing the basic parent structure in livestock in terms of these two compounds. These residues should be included in the dietary exposure assessment.

In drinking water, only pyraclostrobin needs to be estimated in risk assessment. Although BF500-3, BF500-6, and BF500-7 were formed in the laboratory studies, these metabolites are quite immobile and strongly adsorbed to sediments. None of the other degradates are likely to pose significant concern.

For rotational crops, pyraclostrobin and its desmethoxy metabolite are the residues of concern in both the tolerance and risk assessment.

C. Individuals in Attendance

1. Metabolism Assessment Review Committee

C. Olinger, A. Khasawinah, Y. Donovan, A. Protzel, S. Piper, N. Birchfield (EFED)

2. MARC Members in Absentia

J. Doherty, R. Loranger, W. Wassell (comments through email), D. Nixon

3. Presenting Scientists

A. Al-Mudalla, G. Dannan, L. Cheng (MARC member)

4. Other Scientists

J. Bazuin (RD); S. Ramasamy (EFED); P. Leung, R. Reed, J. Gee (CDPR); L. Lang, A. Ally, M. Thomas (PMRA)

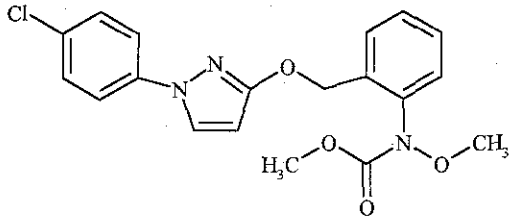
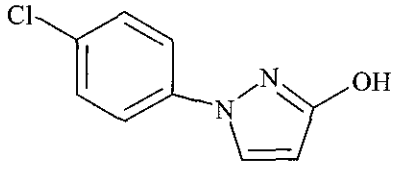
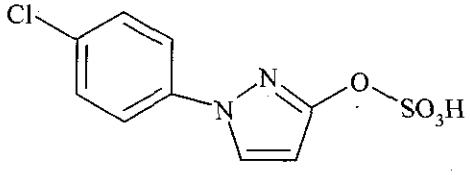
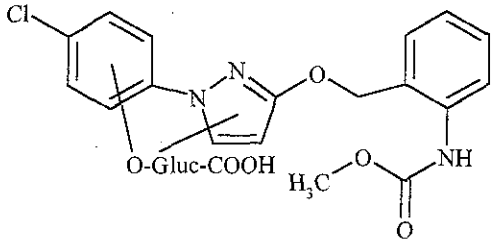
Attachment: 10 pages of structures

cc:RAB3 Reading F, Cheng, MARC (Y. Donovan)

ATTACHMENT

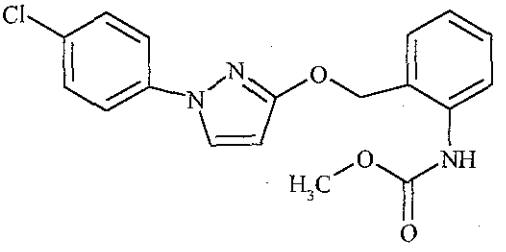
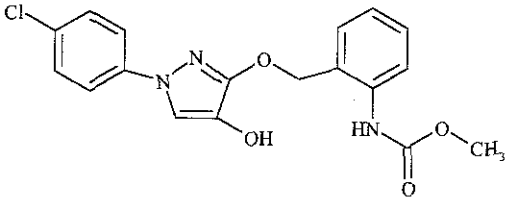
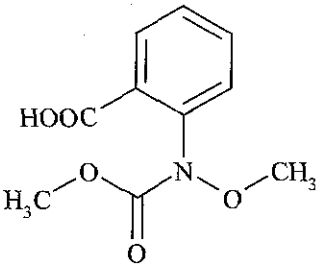
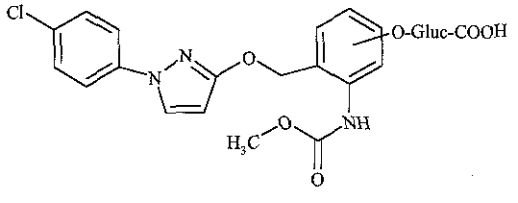
Figure 1: Chemical names and structures of pyraclostrobin and its metabolites identified in plant and animal metabolism studies and confined rotational crop studies.

Figure 1. Chemical names and structures of pyraclostrobin and its metabolites in plant, animal, and rotational crop commodities.

Common name/code Chemical name	Chemical structure	Matrices
Pyraclostrobin; BAS 500 F [Carbamic acid, [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl] phenyl]methoxy-, methyl ester]		Grapes Potato foliage and tubers Wheat forage, grain, and straw Rotational Crops: 30-PBI radish roots and tops, and wheat forage and straw; 120-PBI wheat forage and straw; and 365-PBI wheat straw [a] Goat milk, muscle, fat, liver, and kidney [a] Poultry eggs and fat
BF 500-5; 500M04 1-(4-Chlorophenyl)-1H-pyrazol-3-ol		Potato foliage and tubers [b] Wheat forage, straw, and grain [c] Poultry eggs, fat, and liver Goat milk, liver, and kidney
500M05		Goat milk, liver, and kidney
500M06		Poultry eggs and liver

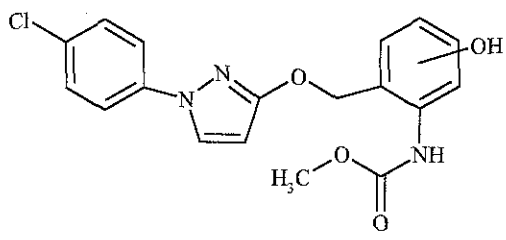
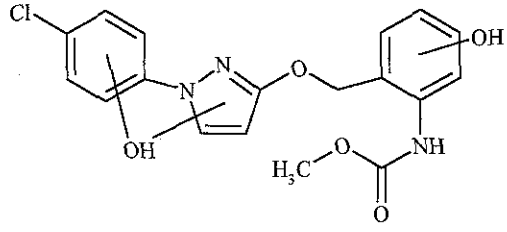
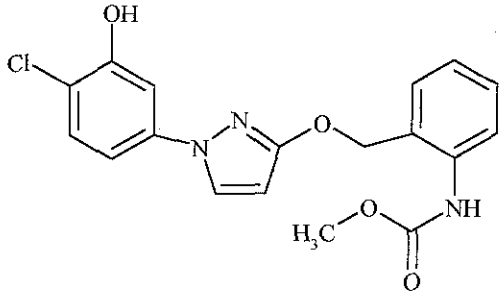
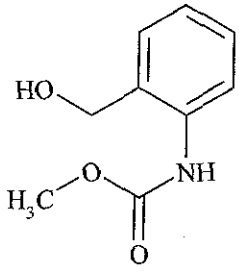
(continued; footnotes follow)

Figure 1 *(continued)*.

Common name/code Chemical name	Chemical structure	Matrices
BF 500-3; 500M07 Methyl-N-[[[1-(4-chlorophenyl)pyrazol-3-yl]oxy]o-tolyl carbamate		Grapes Potato foliage and tubers Wheat forage, grain, and straw Rotational Crops: 30-PBI radish roots and tops, and wheat forage and straw; 120-PBI wheat forage and straw; and 365-PBI wheat straw [a] Goat milk, muscle, fat, liver, and kidney [a] Poultry eggs and fat
500M08		Goat milk and liver
500M24		Wheat grain
500M32		Poultry liver

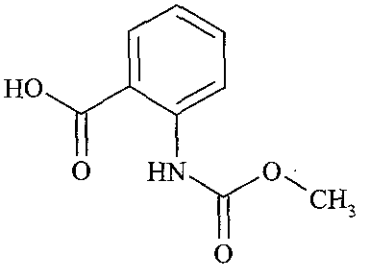
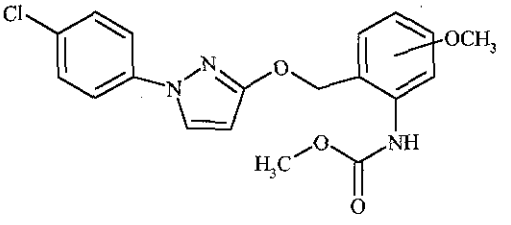
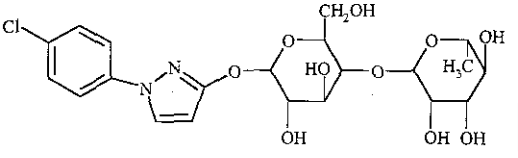
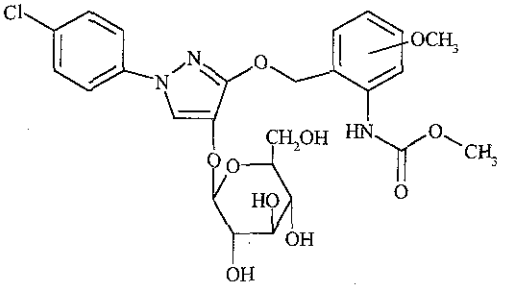
(continued; footnotes follow)

Figure 1 *(continued)*.

Common name/code Chemical name	Chemical structure	Matrices
500M34		Wheat forage and straw
500M39		Goat liver Poultry eggs and liver
500M45		Goat milk and liver
500M49		Poultry eggs, fat, and liver

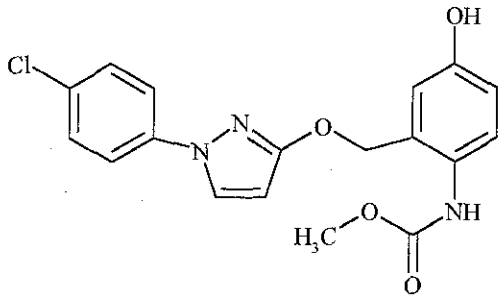
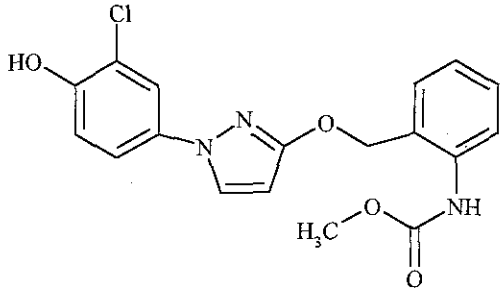
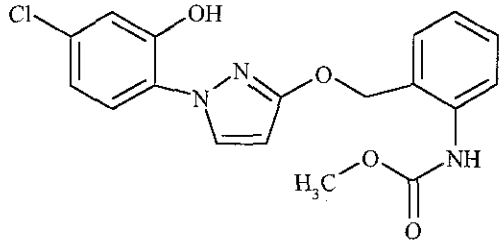
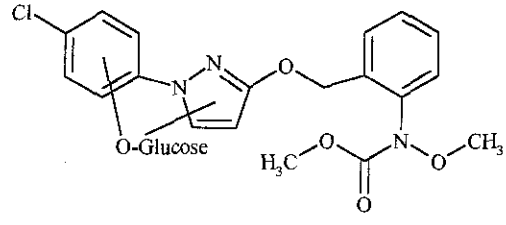
(continued; footnotes follow)

Figure 1 *(continued)*.

Common name/code Chemical name	Chemical structure	Matrices
500M51		Goat kidney
500M54		Grapes Potato foliage and tubers Wheat forage and straw
M55		Grapes
M56		Grapes

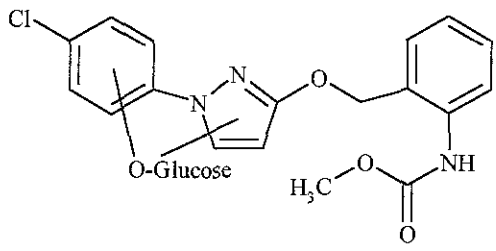
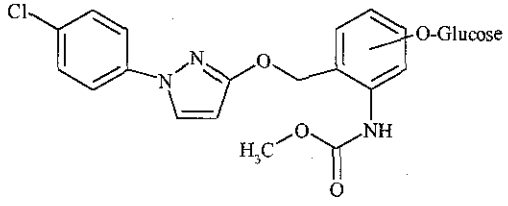
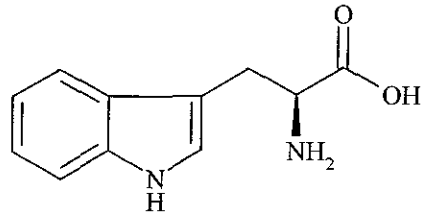
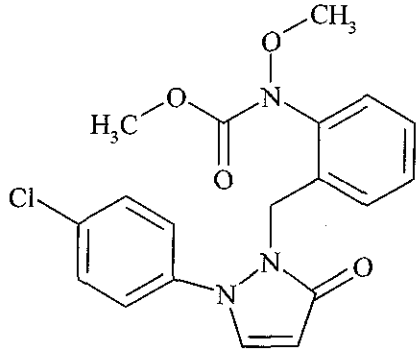
(continued; footnotes follow)

Figure 1 *(continued)*.

Common name/code Chemical name	Chemical structure	Matrices
500M64		Goat milk and kidney Poultry eggs, fat, and liver
500M66		Goat milk, liver, and kidney Poultry liver
500M67		Goat milk, liver, and kidney
500M68		Potato foliage and tubers [b] Wheat forage, straw, and grain [c, d]

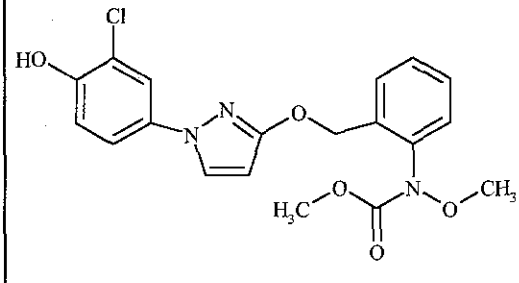
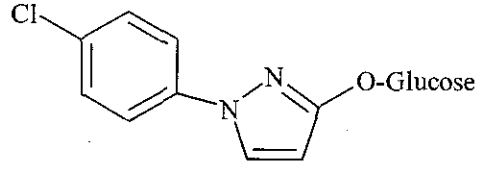
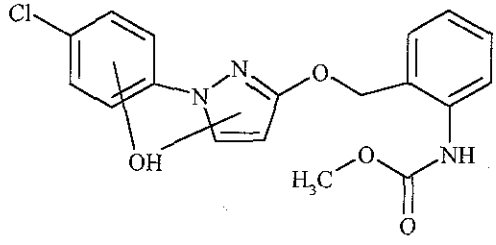
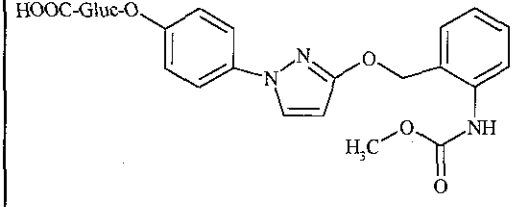
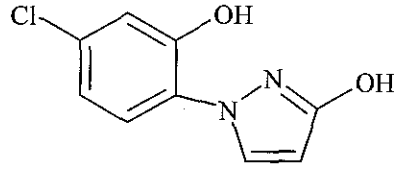
(continued; footnotes follow)

Figure 1 *(continued)*.

Common name/code Chemical name	Chemical structure	Matrices
500M70		Wheat forage, straw, and grain [c, d]
500M71		Wheat forage, straw, and grain [c, d]
500M72; Tryptophan		Potato tubers Wheat grain
500M76		Wheat forage, straw, and grain [c]

(continued; footnotes follow)

Figure 1 *(continued)*.

Common name/code Chemical name	Chemical structure	Matrices
BF 500-16; 500M77 Methyl N-[2-((1-(3-chloro-4-hydroxyphenyl)-1H-pyrazol-3-yl)oxymethyl)phenyl] N-methoxy carbamate		Poultry eggs, fat, and liver
500M79		Potato foliage and tubers
500M80		Poultry liver
500M83		Poultry liver
BF 500-8; 500M85 1-(4-Chloro-2-hydroxyphenyl)-1H-pyrazol-3-ol		Goat milk, liver, and kidney

[a] Pyraclostrobin and metabolite 500M07 co-eluted in goat milk and kidney, and in the rotational crops radish roots and tops, and wheat forage and straw.

[b] Metabolites 500M04 and 500M68 co-eluted in potato foliage and tubers.

[c] Metabolites 500M04 and 500M76, and glucosides 500M68, 500M70, and 500M71 co-eluted in wheat grain.

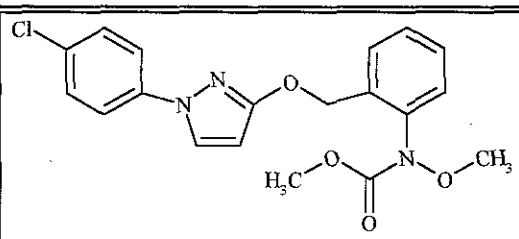
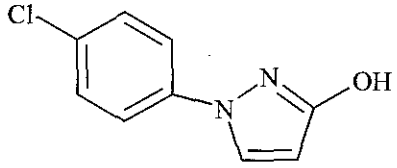
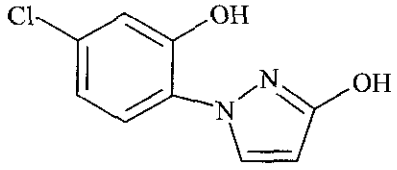
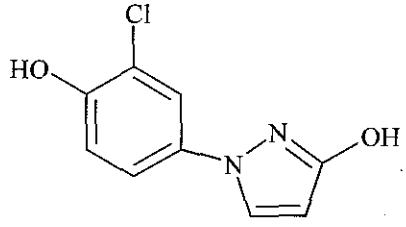
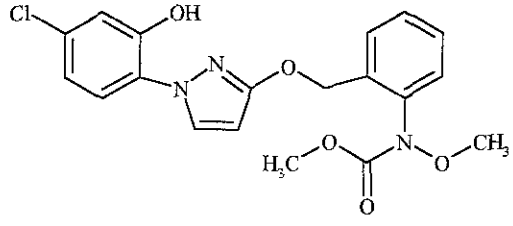
Figure 1 *(continued)*.

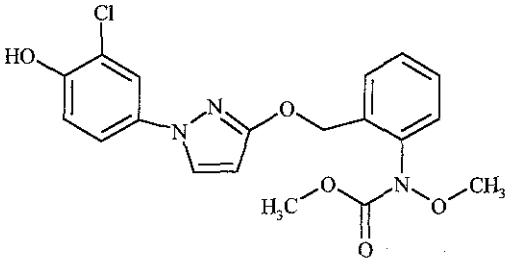
[d] Glucosides 500M68, 500M70, and 500M71 co-eluted in wheat forage and straw.

ATTACHMENT

Figure 2: Chemical names and structures of compounds used in animal commodity analytical methods.

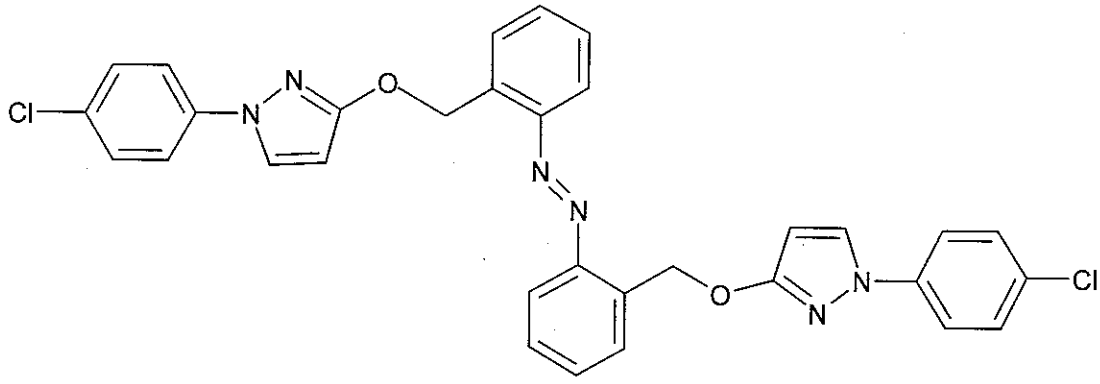
Figure 2: Chemical names and structures of compounds used in animal commodity analytical methods.

Common name/code Chemical name	Chemical structure	Comment
Pyraclostrobin; BAS 500 F [Carbamic acid, [2-[[[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy]methyl] phenyl]methoxy-, methyl ester]		Parent compound
BF 500-5 1-(4-Chlorophenyl)-1H-pyrazol-3-ol		Hydrolysis product generated and determined in GC/MS method 446/0 and LC/MS/MS methods 446/1 and D9902 [a]
BF 500-8 1-(4-Chloro-2-hydroxyphenyl)-1H-pyrazol3-3-ol		Hydrolysis product generated and determined in GC/MS method 446/0 and LC/MS/MS method 446/1 [a]
BF 500-9 1-(3-Chloro-4-hydroxyphenyl)-1H-pyrazol-3-ol		Hydrolysis product generated and determined in LC/MS/MS method D9902
BF 500-10 Methyl N-[2-((1-(4-chloro-2-hydroxyphenyl)-1H-pyrazol-3-yl)oxymethyl)phenyl] N-methoxy carbamate		Compound used in validation studies as representative of metabolites forming BF 500-8

Common name/code Chemical name	Chemical structure	Comment
BF 500-16 Methyl N-[2-((1-(3-chloro-4-hydroxyphenyl)-1H-pyrazol-3-yl)oxymethyl)phenyl] N-methoxy carbamate		Compound used in validation studies as representative of metabolites forming BF 500-9

[a] In GC/MS method 446/0, this compound is determined as the methyl ether.

BF 500-7



BF 500-6