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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: JULY-13-2005

MEMORANDUM

SUBJECT: **Pinoxaden**: Human Health Risk Assessment for New Active Ingredient; First Uses Proposed on Wheat and Barley. PC Code:147500. DP#310864, DP#311624. PP# 4F6817.

Regulatory Action: Section 3/New Active Ingredient
Risk Assessment Type: Single Chemical Aggregate

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Syngenta has submitted a petition for the establishment of permanent tolerances for residues of pinoxaden and its metabolites, NOA 407854 (M2), SYN 505164 (M4), SYN 502836 (M6) in/on wheat and barley.

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of pinoxaden on wheat and barley.

A summary of the findings and an assessment of human risk resulting from the proposed uses of pinoxaden is provided in this document. The risk assessment was provided by Mary Clock-Rust (RAB1), the residue chemistry review and dietary exposure assessment were provided by

Mohsen Sahafeyan (RAB1), the hazard characterization was provided by William Greear (RAB1), the occupational/residential exposure assessment was provided by Mark Dow (RAB1), and the drinking water assessment was provided by Ibrahim Abdel-Saheb of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Background
Pinoxaden is a new post-emergence herbicide for control of grass weeds in wheat (including durum) and barley. The proposed product is NOA 407855 100 emulsifiable concentrate (EC). The proposed use of pinoxaden is one application per crop season at a rate of 0.036 -0.062 lb active ingredient (a.i.)/acre with a pre-harvest interval (PHI) of 60 days and restricted-entry interval (REI) of 48 hours. The petitioner proposes a zero-day plant back interval (PBI) for wheat and barley and 30-day PBI for other crops. A 30-day pre-grazing interval is also included on the label.

Pinoxaden (NOA 407855) is a representative of the new phenylpyrazolin class of chemicals. The mode of action is the inhibition of the enzyme, acetyl-coenzyme A carboxylase (ACCase). ACCase activity in plants can be attributed to two isoenzymes located in different compartments of the plant cell, the chloroplast and the cytosol. The chloroplastic enzyme is responsible for the *de novo* biosynthesis of all fatty acids in the cell. The malonyl-coenzyme A produced by the cytosolic ACCase is required for fatty acid elongation to form very long-chain fatty acids, and for the biosynthesis of flavonoids and malonylated metabolites. Pinoxaden has been found to inhibit both the chloroplastic and the cytosolic ACCase enzyme in gramineae.

This risk assessment is a joint review with the Pesticide Management Regulatory Agency (PMRA) of Health Canada and HED.

There are no existing tolerances, registered uses (including agricultural or residential uses) or exemptions for pinoxaden.

Hazard Characterization
Pinoxaden has a low order of acute toxicity by the oral, dermal and inhalation routes (Toxicity Categories III or IV). Pinoxaden is irritating to the eye, but is not irritating to the skin. Pinoxaden is not a skin sensitizer. In the subchronic and chronic toxicity study in rats, mice and dogs, food consumption (or food efficiency-mice), body weight and body weight gain were the parameters that were most often affected. In addition, rats and mice often showed kidney effects such as renal tubular basophilia and alterations in urinalysis parameters. In the subchronic rat studies, increased water consumption, increased urine volume and kidney effects were observed. In the subchronic mouse study, one also observed piloerection. In the subchronic dog study, there was fluid feces, vomit, pale and thin appearance, decreased activity, dehydration, cold to touch, and regurgitation, in addition to the decreases in body weight, body weight gain and food consumption. In the chronic toxicity study in dogs, no systemic toxicity was observed at the highest dose tested (HDT; 125 mg/kg/day).

Carcinogenicity was not observed in the rat chronic toxicity/carcinogenicity study. The two carcinogenicity studies in mice (1 via gavage; 1 dietary) were considered to be inadequate for evaluating carcinogenic potential of pinoxaden in mice. The increased mortality resulting from gavage error together with lung involvement confounded the results of the gavage carcinogenicity study in mice. The dosing in the dietary study in mice was considered to be inadequate due to the lack of toxicity in animals at the highest dose tested. HED concluded that

a new cancer study is not needed.

The critical adverse-effect for the overall risk assessment is based on the effects seen in the rabbit developmental toxicity study. Effects observed included morbid condition in one rabbit (mortality), early resorptions, postimplantation loss, abortion, decreased body weights, body weight gains and food consumption. The rabbit is the most sensitive species.

Pinoxaden was not neurotoxic in the acute or the subchronic rat neurotoxicity studies. No quantitative or qualitative evidence of increased susceptibility was seen following *in utero* exposure to rats or rabbits in developmental studies or in the reproduction study. Pinoxaden was mutagenic in two *in vitro* mammalian cytogenetic tests using V79 Chinese Hamster lung fibroblasts cells, but negative in an *in vivo* mammalian cytogenetics (micronucleus) test. Pinoxaden was negative in bacterial and mammalian gene mutation tests and in two unscheduled DNA synthesis (UDS) assays. Pinoxaden was considered to be non-mutagenic based on the overall weight-of-evidence. One metabolite, M3, produced decreases in body weight, body weight gain and food consumption in a 90-day feeding study in rats. It was also hepatotoxic in both sexes and nephrotoxic in males. No evidence of mutagenicity was observed with M3 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay, in an *in vivo* (micronucleus) mammalian cytogenetics assay or in an unscheduled DNA synthesis (UDS) assay. However, M3 was positive in an *in vitro* human lymphocyte cytogenetics assay with and without S9-metabolic activation. In a 90-day feeding study in rats, metabolite M6 produced no toxic effects at the highest dose tested of 978 and 1035 mg/kg/day (limit dose) in male and female rats, respectively. No evidence of mutagenicity was observed with M6 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay or in an *in vitro* mammalian cytogenetics assay. No evidence of mutagenicity was observed with M10 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay, in both *in vitro* and *in vivo* (micronucleus) mammalian cytogenetics assays or in an unscheduled DNA synthesis (UDS) assay. An impurity in pinoxaden (SYN519312), did not produce a mutagenic effect when tested in a bacterial gene mutation assay. There was no indication of endocrine disruption.

More than 90% of the orally gavaged dose was absorbed from the gastrointestinal tract. Approximately, 90% of the absorbed dose was excreted in the urine and feces in 72 hours and excretion was nearly complete in 7 days. Excretion in the urine ranged from 59-78% and in feces 20-25%. Tissue distribution data indicated no significant accumulation in the body. A billiary excretion study did not indicate enterohepatic circulation. No parent compound was detected in the urine, feces or bile. The major metabolite in the urine and feces was the hydrolysis product M2. Major metabolites in the urine were M2 (65%-85%) and M4 (5-13%) and in the feces were M2 (50%-70%) and M4 (25%-35%) depending upon the dose. There were no sex-related differences in the absorption, distribution, excretion or qualitative profile of the metabolites.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision
The critical effect for the overall risk assessment is based on the effects seen in the rabbit developmental toxicity study. Effects observed included morbid condition in one rabbit (mortality), early resorptions, postimplantation loss, abortion, decreased body weights, body weight gains and food consumption. The rabbit is the most sensitive species.

The developmental toxicity study in rabbits was chosen for the acute and chronic reference doses (aRfD and cRfD, respectively) as well as for all other exposure routes and durations. For the population females 13-49 years old, the aRfD was calculated using the developmental no-observed adverse-effect level (NOAEL) of 30 mg/kg/day. The lowest-observed adverse-effects level (LOAEL) of 100 mg/kg/day was based on increased incidence of complete early litter resorption. This study provides the lowest dose attributable to a single-dose developmental effect (increased incidence of early resorptions) applicable to the female 13-49 years of age. An aRfD for the general population was not identified since an endpoint of concern attributable to a single dose effect was not identified in the hazard database. The cRfD (0.3 mg/kg/day) and the risk assessments for all other exposure scenarios were calculated based on the maternal NOAEL of 30 mg/kg/day. The LOAEL of 100 mg/kg/day is based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.

The dermal-absorption is estimated to be 40% based on the results of the *in vivo* dermal penetration study in rats using the EC 100 formulation. The dermal-absorption rate is used for all dermal risk assessments since the NOAEL used for assessment is based on an oral study. HED assumes 100% inhalation absorption.

The CARC concluded that data are inadequate for an assessment of human carcinogenic potential due to the absence of an acceptable mouse carcinogenicity study. Based on the weight of the evidence, HED believes that pinoxaden is not likely to pose a cancer risk. Therefore, an aggregate cancer risk assessment was not performed.

Based on toxicological considerations, and the assumptions used in the exposure assessments, the pinoxaden risk assessment team determined that a 1x special FQPA safety factor (SF) was appropriate. The uncertainty factors (UF) used in determining the RfDs were 100 (10x for intraspecies variation and 10x for interspecies extrapolation). Therefore, the acute and chronic population-adjusted doses (aPAD and cPAD) are equal to the aRfD and cRfD, respectively (PAD=RfD/FQPA SF). The level of concern for all non-dietary exposure durations (short-, intermediate- and long-term) is 100.

Dietary Exposure Assessment

The residues of concern (for tolerance setting and risk assessment) in wheat and barley are pinoxaden, M2, M4 (free and conjugated) and M6. In rotational crops, the residues of concern are pinoxaden, M2, M3 (free and conjugated), M10 and M11. In ruminant livestock, pinoxaden, M2 and M4 (free and conjugated) are the residues of concern. In poultry livestock, pinoxaden, M2, M4 (free and conjugated) and M6 are the residues of concern. In drinking water, the residues of concern are pinoxaden, M2 and M3.

Tolerance-level residues and 100% crop treated were assumed for the dietary risk assessment. As tolerances are based on maximum residues from field trials conducted under highest application rates and the shortest PHI, the dietary risk estimates are considered conservative.

The Tier 1 acute dietary risk assessment (including drinking water) indicates that for all included commodities, the acute dietary risk estimate is below HED's level of concern (<100% of the

aPAD). The resulting risk estimate for females 13-49 years old is 1.5 % of the aPAD at the 95th percentile.

The Tier 1 chronic dietary risk assessment (including water) indicates that for all included commodities, the chronic dietary risk estimates are below HED's level of concern for the general U.S. population and all population subgroups (<100% of the cPAD). The chronic dietary exposure estimate for the general population is 0.9% of the cPAD. The estimate for the highest exposed population subgroup (children 1-2 years old) is 2.1% of the cPAD.

Aggregate Risk
No residential uses are proposed for pinoxaden at this time. Therefore, aggregate risk consists of exposure from food and drinking water sources only. Acute and chronic aggregate risks were assessed by incorporating the drinking water estimates directly into the dietary exposure assessment. Aggregate risk estimates are reported above under *Dietary Exposure Assessment.* Acute and chronic aggregate risks do not exceed HED's level of concern.

Occupational Risk
Based upon the proposed use pattern, HED believes the most highly-exposed occupational pesticide handlers (i.e., mixers, loaders, applicators) are:
1) Mixer/loader using open-pour loading of liquids in support of aerial operations
2) Applicator using open-cab ground-boom equipment
3) Aerial applicator (pilot).

Short- (1-30 days) and intermediate-term (1-6 months) exposures were assessed. Although the proposed labeling directs users not to apply more than one application per year, commercial applicators may experience intermediate-term exposures since they may treat a number of farms sequentially.

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in Pesticide Handlers Exposure Database (PHED; v. 1.1, 1998). It is HED policy to assess handler exposure and risk using "baseline" personal protective equipment (PPE) which is comprised of long-sleeved shirt, long pants, and shoes plus socks. If necessary, HED assesses risk using "baseline" plus the use of protective gloves or other PPE as might be necessary or appropriate. The proposed label directs applicators and other handlers to wear a long-sleeved shirt and long pants, shoes plus socks and chemical resistant gloves.

Short- and intermediate-term handler risks were estimated for handlers and postapplication workers. A dermal-absorption factor of 40% was used to calculate occupational risks. HED assumed 100% inhalation absorption.

Provided that mixer/loaders use protective gloves as specified on the proposed label, all margins of exposure (MOEs) are ≥100 and therefore do not exceed HED's level of concern (MOE of at least 100).

There is a potential for agricultural workers to have post-application exposure to pesticides

during the course of typical agricultural activities. Based upon the proposed use pattern (early post-emergence), the most conservative transfer coefficient (TC) applicable to pinoxaden is for scouting at 100 cm^2/hr. Short-term exposures are expected. Post-application worker exposure is estimated using the highest proposed application rate and a TC of 100 cm^2/hr. This TC was obtained from an interim TC policy developed by HED's Science Advisory Council for Exposure (ExpoSAC) using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (SOP # 3.1).

Lacking compound-specific dislodgeable foliar residue (DFR) data, HED assumes 20% of the application rate is available as DFR on day zero after application, adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000). The estimated MOE for postapplication workers is 65,000 and does not exceed HED's level of concern (MOE of at least 100).

HED Recommendations
Provided a revised Section F is submitted, and the Agency validations of the proposed analytical enforcement methods are successful, HED concludes there are no residue chemistry data requirements that would preclude the establishment of a *conditional registration* and the following permanent tolerances:

1) For the combined residues of **pinoxaden** (8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7H-pyrazolo[1,2-d][1,4,5] oxadiazepin-9-yl 2,2-dimethylpropanoate), and its metabolites 8-(2,6-diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione **(M2)**, and free and conjugated forms of 8-(2,6-diethyl-4-hydroxymethyl-phenyl)-tetrahydro-pyrazolo[1,2-d][1,4,5] oxadiazepine-7,9-dione **(M4)**, and 4-(7,9-dioxo-hexahydro-pyrazolo[1,2-d] [1,4,5]oxadiazepin-8-yl)-3,5-diethyl-benzoic acid **(M6)**, calculated as pinoxaden, in/on the following commodities:

Wheat, grain	1.3 ppm
Wheat, forage	3.5 ppm
Wheat, hay	2.0 ppm
Wheat, bran	3.0 ppm
Wheat, straw	1.5 ppm
Barley, grain	0.9 ppm
Barley, hay	1.5 ppm
Barley, straw	1.0 ppm
Barley, bran	1.6 ppm
Egg	0.06 ppm
Poultry, fat	0.06 ppm
Poultry, meat	0.06 ppm
Poultry, meat byproduct	0.06 ppm

2) For the combined residues of **pinoxaden**, and its metabolites **M2**, and free and conjugated forms of **M4**, calculated as pinoxaden, in/on the following commodities:

Milk	0.02 ppm
Cattle[1], fat	0.04 ppm
Cattle[1], meat	0.04 ppm
Cattle[1], meat by product	0.04 ppm

1. Includes sheep, horse, goat and hog.

HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following residue chemistry data:

- Additional storage stability data for wheat and barley processed fractions.
- Additional validation data for pinoxaden and M2 residues in livestock commodities (ruminant and poultry)

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

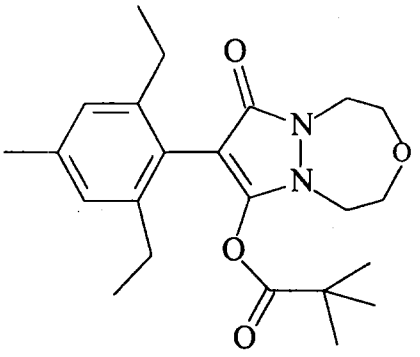
Table 2.1 Summary of Directions for Use of Pinoxaden

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Wheat (including durum) and Barley						
Ground and aerial applications. Foliar spray. Ground: Water volume of 5-10 gals./A.Aerial: Water volume of minimum of 3-5 gals./A.	NOA 407855 100 EC	0.036 -0.062	1	0.062	60	- Pre-grazing Interval of 30 days -Timing: From the 2-leaf stage to pre-boot stage of wheat and barley. Label Recommendations:- Do not treat spring wheat, durum wheat or barley underseeded to forages. Tank mixing is not recommended with any chemical additives, pesticides, or fertilizers that are not recommended on this label. Rotational Crop Restrictions: Wheat (including durum) and barley: 0 days All other crops: 30 days

PHI = pre-harvest interval

2.2 Structure and Nomenclature

Table 2.2 Pinoxaden Nomenclature

Compound	
Common name	pinoxaden
Company experimental name	NOA 407855 or M1
IUPAC name	8-(2,6-diethyl-p-tolyl)-1,2,4,5-tetrahydro-7-oxo-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-9-yl 2,2-dimethylpropionate
CAS name	8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7H-pyrazolo[1,2-d][1,4,5] oxadiazepin-9-yl 2,2-dimethylpropanoate
CAS #	243973-20-8, 99607-70-2
End-use product/EP	NOA 407855 100 EC
Known Impurities of Concern	None

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Pinoxaden

Parameter	Value
Melting point/range	120.5 - 121.6 °C
pH	4.9 at 25 °C
Density (20°C)	1.16 x 103 kg/m3 at 24 °C
Water solubility (20°C)	200 mg/L
Solvent solubility (g/100 mL at 20°C)	acetone 250 dichloromethane >500 ethyl acetate 130 hexane 1.0 methanol 260 octanol 140 toluene 130
Vapor pressure at 20°C and 25°C	2.0 x 10-7 Pa at 20°C4.6 x 10-7 Pa at 25°C
Octanol/water partition coefficient Log(K_{OW}) at 20°C	3.2 at 25°C
UV/visible absorption spectrum	Conditions / λ, nm neutral solution 210, 258 acidic solution 210, 254 basic solution 220, 252 No absorption maximum between 350 and 750 was observed in any of the three solutions.

All data came from PMRA Lab Services.

3.0 Metabolism Assessment

See Appendix 3 (Table A-3.1b) for metabolite structures.

3.1 Comparative Metabolic Profile

In both plant and livestock, pinoxaden undergoes hydrolysis of the ester moiety, hydroxylation and conjugation with sugars. For the most part (in most of the metabolites identified), it appears that the three-ring backbone of pinoxaden is conserved in plants and livestock metabolites.

In plants, pinoxaden is rapidly metabolized to its ester hydrolysis product, M2, which subsequently, at a lower rate, is metabolized to M4 which has an additional hydroxyl group on the phenyl side chain. The free and conjugated form of M4 was identified as the predominate metabolite in all wheat commodities. M6 is also one of the major metabolites in wheat grain.

In confined rotational crops, no substantive variation in the metabolic degradation of pinoxaden was observed. Pinoxaden was hydrolyzed rapidly (disappeared by day 3) in soil, yielding M2. M2 was further hydroxylated forming M3, the predominant metabolite observed in soil. M3 could thus be taken up from the soil by rotated crops. Metabolism of pinoxaden in rotational crops occurred mainly by hydroxylation processes. Other major metabolites were M10 and M11. No quantifiable residues of pinoxaden and/or its metabolites were found in all rotational crops at various PHIs (lettuce, mustard leaves, radish and turnip), except wheat forage and fodder.

In livestock, goats and hens were fed either pinoxaden and/or M4 separately. The major metabolites were M2 and intact M4, with M6 is also seen in hens.

The metabolism of pinoxaden in rats primarily involves the initial hydrolysis of the ester moiety to form metabolite M2 (NOA 407854), which is then extensively excreted in the urine and feces. To a minor extent, metabolite M2 is also further metabolized via hydroxylation, dealkylation, ring cleavage, ring formation, and conjugation into a wide variety of minor metabolites. The proposed pathway is also supported by the appended *in vitro* study, which indicates that pinoxaden is rapidly hydrolyzed to M2 in rat plasma ($T_{½}$ = ~0.1 min) at concentrations up to 100 µM (~40 ppm).

Overall, it can be said that residues of pinoxaden and M4 (and by inference all metabolites sharing a similar structure), have a very low transfer into the edible tissues and milk of lactating goats.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

The metabolism of pinoxaden proceeded predominantly by hydrolysis of the ester moiety of the parent molecule to give M2, which was subsequently hydroxylated either at the 4-methyl group of the phenyl moiety yielding M4, or at position 3 of the pyrazol moiety yielding M3. M3 was further hydroxylated to M10. M4 and M10 were conjugated with glucose leading to M5 and M8. M7 and M9 resulted, respectively, from the malonylation of M5 and M8. Another metabolic pathway resulted from the oxidation of the methyl-hydroxy function of M4 and M10 to the corresponding carboxylic acids M6 and M11. A minor metabolic pathway resulted from the oxidation of the ethyl side chain of M10 followed by cyclisation to M32.

3.2.2 Description of Livestock Metabolism

Transfer of radioactive residues to edible tissues and milk is minimal. In goats administered the predominant plant metabolite M4, transfer of total radioactive residues to milk and edible tissues was very low. The highest concentrations of total radioactive residues in both studies were in the liver and kidney, which is to be expected considering the rapid metabolism and excretion of pinoxaden and its metabolites. These results indicate that residues of pinoxaden and M4 (and by inference all metabolites sharing a similar structure), have a very low transfer into the edible tissues and milk of lactating goats. Overall, it can be concluded that pinoxaden is rapidly metabolized in all lactating goat matrices.

[Phenyl-^{14}C]-pinoxaden was rapidly and completely metabolized in all goat matrices. The parent metabolite was not detected in milk, feces, urine or any of the tissues analyzed. The predominant metabolite identified in all goat matrices was M2, which is formed by the hydrolysis of the ester moiety on the parent molecule. In the [7-^{14}C] M4 metabolism study, the predominant metabolite identified in all goat matrices was unchanged M4. Hydroxylation of M4 to M10 did occur in all matrices characterized, but this represented only a minor fraction (< 10%) of the TRRs. Of note, the metabolite M10 was not detected in any of the matrices of goats administered [phenyl-^{14}C]-

pinoxaden.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

In confined rotational crops, no substantive variation in the metabolic degradation of pinoxaden was observed. Pinoxaden was hydrolyzed rapidly (disappeared by day 3) in soil yielding M2. M2 was further hydroxylated forming M3 the predominant metabolite observed in soil. M3 could thus be taken up from the soil by the rotated crops. Metabolism of pinoxaden in rotational crops occurred mainly by hydroxylation processes. Other major metabolites were M10 and M11. No quantifiable residues of pinoxaden and/or its metabolites were found in all rotational crops (lettuce, mustard leaves, radish and turnip) except wheat forage and fodder.

3.3 Environmental Degradation

Hydrolysis of pinoxaden is pH dependent and occurs faster under basic conditions. Aqueous photolysis of pinoxaden is not a major dissipation route when exposed to sunlight. In soil, photolysis is also not a significant pathway for degradation for pinoxaden without hydrolytic degradation.

Acceptable laboratory studies showed that pinoxaden degrades rapidly under aerobic soil metabolism conditions with half-lives ranging from 2 to 3 days, forming the major degradate M2, which degrades further to form the degradate M3.

Under aerobic aquatic conditions, pinoxaden degrades rapidly to M2 (half-life < 1 day) to the major transformation product, M2, with maximums of 96.6%, 16.7% and 103.5% of the applied in water layer, sediment and total system, respectively. M2 was the major product detected in the treated water-sediment systems under both anaerobic and aerobic conditions. The minor transformation product M3 was identified with maximums of 0.3%, 0.1% and 0.4% in water, sediment and total system, respectively. Under aerobic aquatic conditions, more than 86% of applied activity remains (in total system) in form of the major degradate M2.

Volatility is not a significant route of dissipation. The major degradates of pinoxaden (M2 and M3) are considered to be mobile based on Freundlich K_{ads} values ranging from 0.06-128 ml/g, and 0856-0.28 ml/g, respectively, in three test soils (loamy sand, loam, silty clay loam textures).

3.4 Summary of Major Residues in Metabolism Studies for Pinoxaden

Table 3.4 Summary of Major Residues in Metabolism Studies for Pinoxaden

Matrix	Labeled Ring(s)	PHI Range (days)	Application Rate (lb ai/A)	Residues with >10% TRR and >0.01 ppm[4]
Wheat Grain[2]	Phenyl and/or Oxidiazepin	55-67	0.059	Conjugated M4 (0.127 ppm), conjugated M6 (0.022 ppm)
Wheat Forage[2]	Phenyl and/or Pyrazol and/or Oxidiazepin	14-28	0.059	Conjugated M4 (0.97 ppm)
Wheat Forage, tops, ears[2]	Phenyl and/or Pyrazol and/or Oxidiazepin	28-42	0.059	Conjugated M4 (2.11 ppm), M9 (0.0165 ppm),
Goat (12.1 ppm of pinoxaden in diet)	Phenyl	NA	NA	M2 (2.7 ppm, kidney)
Goat (10 ppm of M4 in diet)	Phenyl	NA	NA	M4 (0.032 ppm, kidney)
Poultry (97 ppm of pinoxaden in diet)	Phenyl	NA	NA	M2 (0.041 ppm, liver), M4 (0.11 ppm, liver), M6 (0.28 ppm , liver)
Rotational Crops[1] (spring wheat forage)	Phenyl	PBI=29 DAT Harvest=70 DAT	~0.06 to soil	M3 (0.0237 ppm)
Rotational Crops[1] (spring wheat fodder)	Phenyl and/or Oxadiazepin	PBI=15 DAT Harvest=89 DAP	~0.06 to soil	M3 (0.011 ppm), M10 (~0.01 ppm), M11 (0.024 ppm)

(DAT = day(s) after treatment), DAP = days after planting

1)Other rotational crop studies on lettuce head, mustard leaves, radishes, and turnips at 30-day PBI (which is on the label for other crops than wheat and barley) resulted in each metabolite residue <0.01 ppm.

2) PBI for wheat and barley is 0-day

3) A 30-day after harvest restriction (for any crop-part) for feeding livestock is stated on the proposed label.

3.5 Toxicity Profile of Major Metabolites and Degradates

In a 90-day feeding study in rats, metabolite M3 produced decreases in body weight, body weight gain and food efficiency in both males and females. M3 also caused treatment-related hepatotoxicity in both sexes and nephrotoxicity in males. No evidence of mutagenicity was observed with M3 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay, in both *in vitro* and *in vivo* (micronucleus) mammalian cytogenetics assays or in an unscheduled DNA synthesis (UDS) assay. However, M3 was positive in an *in vitro* human lymphocyte cytogenetics assay with and without S9-metabolic activation. In a 90-day feeding study in rats, metabolite M6 produced no toxic effects at the highest dose tested of 978 and 1035 mg/kg/day (limit dose) in male and female rats, respectively. No evidence of mutagenicity was observed with M6 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay or in an *in vitro* mammalian cytogenetics assay. No evidence of mutagenicity was observed with M10 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay, in both *in vitro* and *in vivo* (micronucleus) mammalian cytogenetics assays or in an unscheduled DNA synthesis (UDS) assay. An impurity in pinoxaden (SYN519312) , did not produce a mutagenic effect when tested in a bacterial gene mutation assay.

Table 3.5a Toxicity Profile for Pinoxaden Metabolite M3

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-day rats - diet	46203240, 46203231, 46203233 (2003) Acceptable/Guideline 0/0, 15.0/15.2, 99.2/98.8 or 600.6/645.4 mg/kg/day	NOAEL = 99.2/98.8 mg/kg/day (M/F) LOAEL = 600.6/645.4 mg/kg/day based on decreased body weight and body weight gain and food efficiency in both sexes, and evidence of hepatotoxicity in both sexes and nephrotoxicity in males (M/F).
870.5100 *In Vitro* bacterial gene mutation *S. typhimurium/E. coli*	46203315 (2003) Acceptable/Guideline 100, 200, 500, 1000, 2500 or 5000 µg /plate (+/- activation)	No evidence of mutagenicity in Salmonella strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A. [negative]
870.5300 *In Vitro* mammalian gene mutation (L5178YTK$^{+/-}$)	46203319 (2003) Acceptable/Guideline 0, 125, 250, 500, 1000, 1500 or 2000 µg/mL (+/- activation)	No reproducible significant ($p \leq 0.05$) and/or concentration-dependent increases in mutant frequency were observed at any dose level in the presence or absence of S9. [negative]
870.5375 *In vitro* mammalian cytogenetics human lymphocytes	46203323 (2003) Acceptable/Guideline 0, 50, 100, 250, 500, 750, 1000, 1500, 2000, 2500, 3000, and 3324 µg/mL (+/- activation)	At 1500 µg/mL, NOA 447204 induced increased ($p \leq 0.05$) aberration frequencies (excluding gaps) in the presence of S9 in Trials 1 and 2 (4.5-8.67% treated vs 1.0% solvent control), and in the absence of S9 in Trial 1 (6.5% treated vs 2.0% solvent control) after a 3 hour treatment period and a 17 hour recovery period. The significant increases observed equaled or exceeded the upper limit of the historical control ranges. [positive]

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5395 *In Vivo* mammalian cytogenetics micronucleus mice	46203328 (20030 Acceptable/Guideline 0, 200, 400 or 800 mg/kg	No significant increase in micronucleated polychromatic erythrocytes (MPCEs) was observed in any dose at either 24 or 48 hours post-dosing. The positive control induced the appropriate response. [negative]
870.5550 UDS in mammalian cells	46203326 (2003) Acceptable/Guideline 0, 625 or 1250 mg/kg	There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG ≥5) at 2 or 16 hours post-dosing compared to controls. The positive control induced the appropriate response. [negative]

Table 3.5b Toxicity Profile for Pinoxaden Metabolite M6

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-day rats - diet	46203238, 46203232 (2003) Acceptable/Guideline 0/0, 23.9/26.8, 246.8/266.4 or 977.5/1034.9 mg/kg/day	NOAEL = 977.5/1034.9 mg/kg/day (M/F) LOAEL was not observed
870.5100 *In Vitro* bacterial gene mutation *S. typhimurium/E. coli*	46203316 (2003) Acceptable/Guideline 100, 200, 500, 1000, 2500 or 5000 µg /plate (-/+ activation)	No evidence of mutagenicity in Salmonella strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A. [negative]
870.5300 *In Vitro* mammalian gene mutation ($L5178YTK^{+/-}$)	46203320 (2003) Acceptable/Guideline 0, 125, 250, 500, 1000, 1500 or 2000 µg/mL (-/+ activation)	No reproducible significant ($p \leq 0.05$) and/or concentration-dependent increases in mutant frequency were observed at any dose level in the presence or absence of S9. [negative]
870.5375 *In vitro* mammalian cytogenetics human lymphocytes	46203324 (2003) Acceptable/Guideline 50, 100, 200, 500, 1000, 1500 or2000 µg/mL (-/+ activation)	There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation. [negative]

Table 3.5c Toxicity Profile for Pinoxaden Metabolite M10

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5100 *In Vitro* bacterial gene mutation *S. typhimurium/E. coli*	46224810 (2003) Acceptable/Guideline 100, 200, 500, 1000, 2500 or 5000 µg /plate (-/+ activation)	No evidence of mutagenicity in Salmonella strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A. [negative]
870.5300 *In Vitro* mammalian gene mutation ($L5178YTK^{+/-}$)	46224811 (2003) Acceptable/Guideline 0, 125, 250, 500, 1000, 2000 or 3484 µg/mL (-/+ activation)	No reproducible significant ($p \leq 0.05$) increases in mutant frequency were observed at any dose level in the presence or absence of S9. [negative]
870.5375 *In vitro* mammalian cytogenetics human lymphocytes	46224812 (2003) Acceptable/Guideline 10, 50, 100, 250, 500, 750, 1000, 1500, 2500 or 3484 µg/mL (-/+ activation)	There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation. [negative]
870.5395 *In Vivo* mammalian cytogenetics micronucleus mice	46224813 (2004) Acceptable/Guideline 0 or 2000 mg/kg	No significant increase in micronucleated polychromatic erythrocytes (MPCEs) was observed in any dose at either 24 or 48 hours post-dosing. The positive control induced the appropriate response. [negative]
870.5550 UDS in mammalian cells	46224814 (2004) Acceptable/Guideline 2000 mg/kg	There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG ≥ 5) at 2 or 16 hours post-dosing compared to controls. The positive control induced the appropriate response. [negative]

Table 3.5d Toxicity Profile for Pinoxaden Impurity SYN519312

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5100 *In Vitro* bacterial gene mutation *S. typhimurium/E. coli*	46203317 (2003) Acceptable/Guideline 100, 200, 500, 1000, 2500 or 5000 µg /plate (-/+ activation)	No evidence of mutagenicity in Salmonella strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A. [negative]

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

3.6.1 Tabular Summary

Table 3.6.1 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Wheat+Barley	Pinoxaden, M2, M4 (free & conjugated), M6	Pinoxaden, M2, M4 (free & conjugated), M6
	Rotational Crops	Pinoxaden, M2, M3 (free & conjugated), M10, M11	No tolerance required.
Livestock	Ruminant	Pinoxaden, M2, M4 (free & conjugated)	Pinoxaden, M2, M4 (free & conjugated)
	Poultry	Pinoxaden, M2, M4 (free & conjugated), M6	Pinoxaden, M2, M4 (free & conjugated), M6
Drinking Water		Pinoxaden, M2 and M3	NA

3.6.2 Rationale for Inclusion of Metabolites and Degradates

Plants

The metabolites with >10%TRR and >0.01 ppm in studies with the same or similar proposed use pattern (rate, PHI, ground) were chosen as metabolites of concern since it was determined that all the metabolites of pinoxaden are expected to have similar toxicity level as of the parent. From wheat grain metabolism studies (14C-Phenyl and 14C-oxadiazepin study, PHI: 55-67 days, rate: 66 g ai/ha), the metabolites of concern were M4 (free and conjugated) and M6. Thus, the residues of concern for wheat grain, besides parent and M2 (since parent is rapidly transformed to M2) were determined to be M4 (free and conjugated), and M6. Likewise for wheat forage (from studies with 14-day and 28-day PHIs, 66 g a.i./ha), the metabolites of concern besides parent and M2 were M4 (free and conjugated) and M6. The metabolite M9 was not included since it was detected in only one study.

Livestock

From livestock metabolism studies, the residues with concentrations >10% TRR were chosen as residues of concern for livestock. Therefore, besides the parent compound, M2 and M4 (free and conjugated) for ruminants and M2, M4 (free and conjugated), and M6 for poultry were determined to be residues of concern. M4 is the major metabolite in the livestock. [14C-phenyl]-pinoxaden and [14C-phenyl]-M4 were the only compounds that were fed to ruminants in two separate studies. HED concluded that since in the livestock metabolism studies it was shown that the backbone of pinoxaden which is comprised of 3 rings remains intact in all the metabolites and M4 is the major metabolite, additional studies are not required. The same conclusion was drawn for poultry metabolism study.

Rotational Crops
From rotational crop studies in which ~ 0.06 lb ai/A [14C-phenyl]- or [14C-oxadiazepin]-pinoxaden was applied to soil, with eliminating the residues <0.01 ppm the other observed metabolites, i.e., M2, M3, M10, and M11 (beside the parent) were determined to be residues of concern based on 15 DAT and 30 DAT PBI in rotated spring wheat forage and fodder with restriction of no more than 0.06 lb ai/A use rate on primary crops. No metabolites with concentrations above 0.01 ppm were found in rotated head lettuce, radish (tops and roots), mustard leaves, turnip, and cereal grains at 30 or 15 DAT PBI.

The proposed label specifies a 0-day PBI for cereal grains and a 30-day PBI for other crops; therefore a revision is required. The recommended PBIs are:
0-day PBI for wheat and barley,
30-day PBI for leafy and root crops
120-day PBI for other cereal grains and all other crops.

Drinking Water
In laboratory studies under aerobic soil metabolism conditions or aerobic aquatic conditions, it has been shown that pinoxaden rapidly degrades to M2 and then M3 (half-life of 2-3 days for the parent); therefore, the residues of concern for drinking water are the parent, and metabolites M2 and M3.

4.0 Hazard Characterization/Assessment

The toxicological database for pinoxaden is considered adequate for hazard characterization. Normally, a 28-day inhalation toxicity study would be required. However, based on the low volatility and low inhalation toxicity (Category IV) of pinoxaden and inhalation margins of exposure (MOEs) >1000 for the proposed uses in this risk assessment, pinoxaden qualifies for a waiver of the 28-day inhalation toxicity study for the proposed uses [HED Standard Operating Procedure (SOP) 2002.01: *Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies*, 08/15/02]. **The requirement for the 28-day inhalation toxicity study is waived for this action only.** If in the future, requests for new uses or formulations are submitted that may result in a significant change in either the toxicity profile or exposure scenarios, HED will reconsider this data requirement.

The two mouse carcinogenicity studies (1 via gavage; 1 dietary feeding) were considered to be inadequate for evaluating carcinogenic potential. Nonetheless, based on the following weight-of-evidence, a repeat carcinogenicity study in mice is not required at this time and it is not expected to provide additional useful information for the risk assessment.

- No evidence of carcinogenicity was observed in an acceptable/guideline carcinogenicity study in rats
- The gavage carcinogenicity study in mice was conducted at doses as high as 750 mg/kg/day. No tumors were observed in other organs except adenomas/carcinomas in the lungs. However, the interpretation of the adenomas/carcinomas in the lungs was confounded by the gavage errors that may have introduced the dosing solution in to the trachea and lungs, and perhaps leading to lung tumors and excessive mortality.

- No tumors were seen in the mouse dietary carcinogenicity study, however, the dosing was considered to be inadequate due to the lack of significant systemic toxicity at doses up to 181.2 mg/kg/day (the study, performed under OECD and EPA guidelines, was terminated early for humanitarian reasons due to excessive decreases in body weight gain in the high dose animals)
- In the 90-day feeding study in mice, pinoxaden was tested up to 7000 ppm (1311 mg/kg/day; Limit Dose), and did not produce any tumors or severe toxicity.
- Pinoxaden was considered to be non-mutagenic.

This evidence convinces EPA that repeating the dietary mouse cancer study is unlikely to provide additional useful information for the risk assessment, and that pinoxaden is not likely to pose a cancer risk.

4.1 Hazard Characterization

Pinoxaden has a low order of acute toxicity by the oral, dermal and inhalation routes (Toxicity Categories III or IV). Pinoxaden is severely irritating to the eye, but is not irritating to the skin. Pinoxaden is not a skin sensitizer. In the subchronic and chronic toxicity study in rats, mice and dogs, food consumption (or food efficiency-mice), body weight and body weight gain were the parameters that were most often affected. In addition, rats and mice often showed kidney effects such as renal tubular basophilia and alterations in urinalysis parameters. In the subchronic rat studies, increased water consumption, increased urine volume and kidney effects were observed. In the subchronic mouse study, one also observed piloerection. In the subchronic dog study, fluid feces, vomit, pale and thin appearance, decreased activity, dehydration, cold to touch, and regurgitation were observed, in addition to the decreases in body weight, body weight gain and food consumption. In the chronic toxicity study in dogs, no systemic toxicity was observed at the highest dose tested (HDT; 125 mg/kg/day). Carcinogenicity was not observed in the rat chronic toxicity/carcinogenicity study. The two carcinogenicity studies in mice (1 via gavage; 1 dietary) were considered to be inadequate for evaluating the carcinogenic potential of pinoxaden in mice. The increased mortality resulting from gavage error together with lung involvement confounded the results of the gavage carcinogenicity study in mice. The dosing in the dietary study in mice was considered to be inadequate due to the lack of toxicity in animals at the highest dose tested.

The critical adverse-effect for the overall risk assessment is based on the effects seen in the rabbit developmental toxicity study. Effects observed included morbid condition in one rabbit (mortality), early resorptions, postimplantation loss, abortion, decreased body weights, body weight gains and food consumption. The rabbit is the most sensitive species.

Pinoxaden was not neurotoxic in the acute or the subchronic rat neurotoxicity studies. No quantitative or qualitative evidence of increased susceptibility was seen following *in utero* exposure to rats or rabbits in developmental studies or in the reproduction study. Pinoxaden was mutagenic in two *in vitro* mammalian cytogenetic tests using V79 Chinese Hamster lung fibroblasts cells, but negative in an *in vivo* mammalian cytogenetics (micronucleus) test. Pinoxaden was negative in bacterial and mammalian gene mutation tests and in two unscheduled DNA synthesis (UDS) assays. Pinoxaden was considered to be non-mutagenic based on the overall weight-of -evidence. One metabolite, M3, produced decreases in body weight, body

weight gain and food consumption in a 90-day feeding study in rats. It was also hepatotoxic in both sexes and nephrotoxic in males. No evidence of mutagenicity was observed with M3 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay, in an *in vivo* (micronucleus) mammalian cytogenetics assay or in an unscheduled DNA synthesis (UDS) assay. However, M3 was positive in an *in vitro* human lymphocyte cytogenetics assay with and without S9-metabolic activation. In a 90-day feeding study in rats, metabolite M6 produced no toxic effects at the highest dose tested of 978 and 1035 mg/kg/day (limit dose) in male and female rats, respectively. No evidence of mutagenicity was observed with M6 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay or in an *in vitro* mammalian cytogenetics assay. No evidence of mutagenicity was observed with M10 when tested in an *in vitro* bacterial gene mutation assay, in an *in vitro* mammalian gene mutation assay, in both *in vitro* and *in vivo* (micronucleus) mammalian cytogenetics assays or in an unscheduled DNA synthesis (UDS) assay. An impurity in pinoxaden (SYN519312), did not produce a mutagenic effect when tested in a bacterial gene mutation assay. There was no indication of endocrine disruption.

More than 90% of the orally gavaged dose was absorbed from the gastrointestinal tract. Approximately, 90% of the absorbed dose was excreted in the urine and feces in 72 hours and excretion was nearly complete in 7 days. Excretion in the urine ranged from 59-78% and in feces 20-25%. Tissue distribution data indicated no significant accumulation in the body. Billiary excretion study did not indicate enterohepatic circulation. No parent compound was detected in the urine, feces or bile. Major metabolite in the urine and feces was the hydrolysis product M2. Major metabolites in the urine were M2 (65%-85%) and M4 (5-13%) and in the feces 50%-70%) and M4 (25%-35%) depending up on the dose. There were no sex related differences in the absorption, distribution, excretion or qualitative profile of the metabolites. Toxicology data generated on several metabolites and one contaminant of pinoxaden are summarized in Table 3.5 a-d.

Table 4.1a: Acute Toxicity Profile - Pinoxaden

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	46203214	LD_{50} >5000 mg/kg	IV
81-2	Acute Dermal	46203219	LD_{50} > 2,000 mg/kg (limit dose)	III
81-3	Acute Inhalation	46203221	LC_{50} = 5.22 mg/L	IV
81-4	Primary Eye Irritation	46203223	Severe eye irritant	I
81-5	Primary Skin Irritation	46203225	Non-irritating	IV
81-6	Dermal Sensitization	46203227	Non sensitizer	n/a

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - Pinoxaden

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day rats - gavage	46203239 (2003) Acceptable/Guideline 0, 3, 10, 30, 100, or 300 mg/kg/day	NOAEL = 300/100 mg/kg/day (M/F) LOAEL was not observed in males; = 300 mg/kg/day in females, based on increased water consumption and urinary volume
870.3100 90-Day rats - diet	46203235, 46203237 (2003) Acceptable/Guideline 0, 150, 1000, 5000, or 10000 ppm (0/0, 15/16, 98/110, 466/527 or 900/965mg/kg/day in males/females)	NOAEL = 466/537 mg/kg/day (M/F) LOAEL = 900/965 mg/kg/day based on decreased body weight and body weight gain and increased incidence of renal lesions in both sexes; decreased food consumption and increased water consumption in males; and increased urine volume in females
870.3100 13-Week oral mice - gavage	46203241 (2002) Acceptable/Guideline 0, 10, 100, 400, 700 or 1000 mg/kg/day (limit dose)	NOAEL = 700 mg/kg/day LOAEL = 1000 mg/kg/day based on increased incidence of piloerection and decreased body weight gain in both sexes, and increased incidence of renal tubular basophilia in males
870.3100 90-Day oral mice - diet	46203236, 46224805 (2003) Acceptable/Guideline 0, 1000, 2500, 5000 or 7000 ppm (0/0, 140.9/165.9, 365.0/436.7, 708.2/900.6 or 992.3/1311.7 mg/kg/day in males/females)	NOAEL was not observed in females, but was 365.0 mg/kg bw/day in males LOAEL =165.9 mg/kg bw/day in females, based on decreased body weight and body weight gain and 708.2 mg/kg bw/day in males, based on decreased food efficiency
870.3150 90-Day dogs - capsule	46203242 (2003) Acceptable/Guideline 0, 25, 100, 250 or 500 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day based on clinical signs of toxicity fluid feces, vomit, pale and thin appearance, decreased activity, dehydration, cold to touch, and regurgitation in both sexes, and mucus in feces in the males) and decreased body weights, body weight gains, and food consumption in both sexes
870.3200 28-Day dermal toxicity - rat	46203243 (2001) Acceptable/Guideline 0, 10, 100, or 1000 mg/kg/day	LOAEL was not observed NOAEL = 1000 mg/kg bw/day (the limit dose)
870.3700 Prenatal developmental toxicity - rabbit	46203303 (2003) Acceptable/Guideline 0, 3, 10, 30, or 100 mg/kg/day	Maternal NOAEL = 30 mg/kg/day Maternal LOAEL = 100 mg/kg/day, based on increased mortality, abortion, and decreased body weights, body weight gains and food consumption Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = 100 mg/kg day, based on increased incidence of complete early litter resorption
870.3700 Prenatal developmental toxicity - rat	46203305 (2003) Acceptable/Guideline 0, 3, 30, 30, 300 or 800 mg/kg/day	Maternal NOAEL = 30 mg/kg/day Maternal LOAEL = 300 mg/kg bw/day, based on decreased body weight gains and food consumption Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = 300 mg/kg/day, based on delays in skeletal ossification in the skull and hind digits

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects - rat	46203308 (2003) Acceptable/Guideline 0, 10, 50, 250 and 500 mg/kg/day	Parental NOAEL = 250 mg/kg/day Parental LOAEL = 500 mg/kg/day, based on increased water consumption, renal tubular atrophy, and chronic nephropathy in both sexes, and increased incidence of renal pelvic dilatation in the males Offspring NOAEL = 250 mg/kg/dy Offspring LOAEL = 500 mg/kg bw/day, based on decreased body weights and body weight gains in the F_1 pups, and decreased body weights in the F_2 males Reproductive NOAEL = 500 mg/kg/day Reproductive LOAEL was not observed
870.4100 Chronic toxicity dogs - capsule	46203309 (2003) Acceptable/Guideline 0, 5, 25 or 125 mg/kg/day	NOAEL = 125 mg/kg/day LOAEL was not observed
870.4200 Carcinogenicity mice - diet	46448801 (2004) Unacceptable/Guideline 0, 10, 150, 500, 1500 or 4000 ppm (0/0, 16.3/20.2, 60.7/75.7, 181.2/216.5 and 573.7/706.4 mg/kg/day in males/females) [4000 ppm dose discontinued at Week 40]	NOAEL = 216.5/181.2 mg/kg/day (M/F) LOAEL was not determined
870.4200 Carcinogenicity mice- gavage	46224808 (2003) Unacceptable/Guideline 0, 5, 40, 300 or 750 mg/kg	NOAEL/LOAEL could not be determined. The study could not be interpreted due to gavage errors and lung involvement.
870.4300 Chronic toxicity/carcino genicity rats - gavage	46224809 (2003) Acceptable/Guideline 0, 1, 10, 100 250 or 500 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day, based on mortality, clinical signs, and increased serum urea and creatinine in males, and decreased body weights and body weight gains, increased water consumption and incidence of urinalysis findings, kidney surface granulation, and microscopic renal lesions in both sexes
870.5100 *In Vitro* bacterial gene mutation *S. typhimurium/E. coli*	46203314 (2001) Acceptable/Guideline 33, 100, 333, 1000, 2500, or 5000 µg/plate w/wo activation (cytotoxicity was observed at ≥1000 µg/plate)	No marked increases in the number of revertants were observed at any concentration in any strain in either trial. [negative]
870.5300 *In Vitro* mammalian gene mutation (L5178YTK$^{+/-}$)	46203318 (2003) Acceptable/Guideline 6.3, 12.5, 254200 µg/mL (-S9) and 3.1, 6.3, 12.5, 25, 50, 100 or 150 µg/mL (+S9)	No reproducible substantial (≥2x solvent controls) and/or concentration-dependent increases in mutant colonies per 10^6 cells were observed at any dose level in the presence or absence of S9. [negative]

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.5375 *In vitro* mammalian cytogenetics in V79 Chinese Hamster Lung Fibroblasts	46203321(2001) Acceptable/Guideline 6.3, 10, 12.5, 20, 25, 40, 50, 60, 75, 80 or 100 µg/mL 10, 20, 40, 60, 80, or 100 µg/mL (-S9); 10, 12.5, 20, 25, 30, 40, 50, 60, 70, 75, 80, 100 or 120 µg/mL (+S9)	Although there was not a clear dose-response and several of the increases in percent aberrant cells were within the historical control range (0.0-4.0%), there was sufficient reproducible evidence of a positive mutagenic effect in the presence and absence of S9. [positive]
870.5375 *In vitro* mammalian cytogenetics in V79 Chinese Hamster Lung Fibroblasts	46203322 (2002) Acceptable/Guideline 10, 15, 20, 30, 40, 45, 60, 75, 80, 90 and 100 µg/mL (-S9); 3.8, 7.5, 15, 30, 45, 60 and 90 µg/mL (+S9)	There was an increase in the percent aberrant cells that exceeded the historical control range with/without S9 metabolic activation. [positive]
870.5395 *In Vivo* mammalian cytogenetics micronucleus mice	46203325 (2002) Acceptable/Guideline 2000 mg/kg (bone marrow toxicity was not induced)	There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG ≥5) at 2 or 16 hours post-dosing compared to controls. [negative]
870.5550 UDS in mammalian cells	46203329 (2001) Acceptable/Guideline 0, 1.17, 2.34, 4.69, 9.38, 18.75, 37.5, 75, 150, 300, or 600 µg/mL (cytotoxic levels ≥300 µg/mL)	There were no marked increases observed in the mean grains per nucleus or mean NNG in either trial. Negative for increased UDS up to limit dose. [negative]
870.5550 UDS in mammalian cells	46203325 (2002) Acceptable/Guideline 2000 mg/kg	There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG ≥5) at 2 or 16 hours post-dosing compared to controls. [negative]
870.6200 Acute neurotoxicity rats - gavage	46203331, 46203330 (2003) Acceptable/Guideline 0, 100, 500 or 2000 mg/kg	NOAEL = 2000 mg/kg (for neurotoxicity) LOAEL was not determined.
870.6200 Subchronic neurotoxicity rats -gavage	46203332 (2003) Acceptable/Guideline 0, 10, 100 or 500 mg/kg/day	NOAEL = 500 mg/kg/day (for neurotoxicity) LOAEL was not determined

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism- Rat	46203333-46203336 (2001) Acceptable/Guideline 0.5 or 300 mg/kg	Approximately 90% of the orally gavaged dose was absorbed from the gastrointestinal tract. Approximately, 90% of the absorbed dose was excreted in the urine and feces in 72 hours and excretion was nearly complete in 7 days. Excretion in the urine ranged from 59-78% and in feces 20-25%. Tissue distribution data indicated no significant accumulation in the body. Billiary excretion study did not indicate enterohepatic circulation. No parent compound was detected in the urine, feces or bile. Major metabolite in the urine and feces was the hydrolysis product M2. Major metabolites in the urine were M2 (65%-85%) and M4 (5-13%) and in the feces 50%-70%) and M4 (25%-35%) depending up on the dose. There were no sex related differences in the absorption, distribution, excretion or qualitative profile of the metabolites.
870.7600 *In Vivo* Dermal penetration- Rat	46203342 (2003) Acceptable/Guideline 0.05, 0.25 or 4.0 mg/rat (EC 100 formulation)	Low dose= 4%, 14%, 18% at 4, 10, 24 hours Mid dose= 1%, 2%, 4% at 4, 10, 24 hours High dose= 17%, 30%, 36% at 4, 10, 24 hours

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The toxicology database for pinoxaden is complete. The following acceptable studies are available:

- Developmental toxicity studies in rats and rabbits
- 2-Generation reproductive toxicity studies in rats
- Acute and Subchronic neurotoxicity studies in rats

4.2.2 Evidence of Neurotoxicity

There is no concern for neurotoxicity resulting from exposure to pinoxaden. Clinical signs (hunched postured, piloerection, decreased activity and/or cold to touch) were sometimes observed in a few rats, mice and dogs at high dose levels. These signs are non-specific in nature, and are sometimes exhibited in compromised animals. Other signs indicative of neurotoxicity [i.e. ataxia, tremors, tilting head, convulsions or altered gait (staggered gait or circling)] were not observed in these or in other studies with pinoxaden.

- In the chronic toxicity/carcinogenicity study in rats (MRID 4624809), an increased incidence of hunched posture was observed in the ≥250 mg/kg/day males (31-38% treated vs 18% controls) and 500 mg/kg/day females (28% treated vs 19% controls). Piloerection was increased in the ≥250 mg/kg/day males (30-41% treated vs 18% controls). The incidences of these signs were significant ($p \leq 0.05$) only in the 250 mg/kg/day males. The petitioner stated that these findings in the males usually occurred in the same week as the animals were found dead or sacrificed *in extremis*. The earliest occurrences of hunched posture were as follows: males at 250 (week 32) and 500 (week

31) mg/kg/day and females at 500 (week 11) mg/kg/day. Piloerection was first observed in the 250 mg/kg/day males at week 64 and in the 500 mg/kg/day males at week 31. There were no other increases in clinical signs of toxicity.

- In the 90-day dog study (MRID 46203242), males and females in the 250 mg/kg/day group had decreased activity and were cold to the touch.

- In the 13-week study in mice (MRID 446203241), at 1000 mg/kg/day piloerection (neck fur raised) was observed at the cageside in both sexes (50-80% treated vs 0-10% controls) and during the functional observation battery(FOB; n=10) at an increased incidence in 2-5 males on weeks 1 and 3-6, and 4 females on week 3 and 1 female on weeks 4 and 9.

1) Rat Acute Neurotoxicity Study (MRID 46203331)

Executive Summary: In an acute oral neurotoxicity study (MRIDs 46203331 and 46203330), pinoxaden (97.2% a.i., Batch # EZ005006) in 0.5% carboxymethylcellulose/0.1% Tween 80 in distilled water was administered in a single-dose by gavage (10 mL/kg) to non-fasted Wistar rats (10/sex/dose) at doses of 0, 100, 500, or 2000 mg/kg (limit dose). All animals were observed for up to 14 days post-dosing. FOB and motor activity were evaluated pretreatment and on days 1 (at approximately 2-3 hours post-dosing), 8, and 15. At termination, 5 rats/sex/group were perfused *in situ* for neurohistological examination. Positive control data were not provided.

No compound-related effects on mortality, clinical signs, body-weight, body-weight gain, food consumption, FOB, motor activity, or gross and histopathology were observed at any dose in either sex.

The LOAEL was not observed. The NOAEL is 2000 mg/kg (limit dose).

No evidence of neurotoxicity was observed.

The study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.6200a; OECD 424) for an acute neurotoxicity screening battery in rats.

2) Rat Subchronic Neurotoxicity Study (MRID 446203332)

Executive Summary: In a subchronic neurotoxicity study (MRID 46203332), pinoxaden (97.2% a.i., Batch # EZ005006) in 0.5% carboxymethylcellulose/0.1% (w/w) Tween 80 in distilled water was administered to 12 Wistar rats/sex/dose via gavage at doses of 0, 10, 100, or 500 mg/kg bw/day for up to 90 days. All animals were evaluated for FOB and motor activity at weeks -1, 2, 5, 9, and 14. At study termination, 5 animals/sex/group were perfused *in situ*, and tissues from the control and 500 mg/kg bw/day groups were examined microscopically. Positive control data were not provided.

Mortality, body-weight, body-weight gain, food consumption and utilization, ophthalmoscopic evaluations, FOB, motor activity, organ weights, gross necropsy, and neuropathology were unaffected by treatment.

Treatment-related effects were limited to salivation and signs of salivation in the ≥100 mg/kg bw/day animals. Salivation was predominantly recorded at clinical examination immediately prior to dosing, and was absent during the FOB (recorded earlier that day). The petitioner stated that these findings were due to a behavioral 'anticipatory' response to the dosing procedure rather than a pharmacological or toxicological response to the test material. The reviewers agree that these findings are likely not toxicologically important; however, the 'anticipatory' response is unlikely due to the dosing procedure itself, otherwise the control and 10 mg/kg bw/day animals would also show evidence of salivation prior to dosing.

The LOAEL was not observed. The NOAEL is 500 mg/kg bw/day.

There was no evidence of neurotoxicity at any dose tested.

The study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.6200b) for a subchronic neurotoxicity study in rats.

4.2.3 Developmental Toxicity Studies

Developmental Toxicity Study in Rats (MRID 46203305)

Executive Summary: In a developmental toxicity study (MRIDs 46203305 and 46203304), pinoxaden (Batch # EZ005006; 97.2% a.i.) in 0.5% (w/w) carboxymethylcellulose + 0.1% (w/w) aqueous Tween 80 was administered daily by oral gavage at a dose volume of 10 mL/kg bw to 24 female Wistar (Hanlbm:WIST [SPF]) rats/group at dose levels of 0, 3, 30, 300, or 800 mg/kg/day on gestation days (GD) 6 through 20. All dams were killed on GD 21; their fetuses were removed by cesarean section and examined.

There were no effects of treatment on gross pathology.

At 300 mg/kg/day, decreases ($p \leq 0.05$) in body-weight gains were observed on GD 6-20 (decreased 12%). Food consumption was also decreased ($p \leq 0.01$) on GD 6-11 and 16-21 (decreased 10%).

At 800 mg/kg/day, 1 dam was killed *in extremis* on GD 17. Prior to death, this animal exhibited respiratory sounds, dyspnea, hunched posture, reduced activity, and piloerection. The death of the dam on GD 17 may be considered as due to treatment. Additionally at this dose, piloerection was observed on GD 15-21 in 2-18/24 rats. Body-weights were decreased ($p \leq 0.05$) on GD 19-21 (decreased 6-10%), and body-weight gains were decreased ($p \leq 0.01$) during treatment (GD 6-21) both uncorrected (decreased 33%) and corrected (decreased 103%) for gravid uterus weight. Gravid uterus weights were also decreased (decreased 12%; $p \leq 0.05$). Food consumption was decreased ($p \leq 0.01$) throughout treatment (GD 6-21; decreased 20-28%).

The maternal LOAEL is 300 mg/kg bw/day, based on decreased body-weight gains and food consumption. The maternal NOAEL is 30 mg/kg bw/day.

There were no abortions, premature deliveries, or dead fetuses. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), or on sex ratio or post-implantation losses. There were no treatment-related external, visceral, or skeletal malformations or variations.

Incomplete ossification of the interparietal bone and metatarsal 1 was observed in the 300 and 800 mg/kg/day groups compared to concurrent and historical controls. Additionally, at 800 mg/kg/day, increased ($p \leq 0.05$) incidence of incomplete ossification of the occipital, parietal, and frontal bones, and unossified hind limb calcaneus, metatarsal 1, and the distal phalanx of posterior digits 2, 3, and 4 were observed compared to concurrent and historical controls. Decreases ($p \leq 0.01$) were also observed in fetal body-weights in both sexes (decreased 6-8%).

The developmental LOAEL is 300 mg/kg bw/day, based on delays in skeletal ossification in the skull and hind digits. The developmental NOAEL is 30 mg/kg bw/day.

This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the guideline requirements for a developmental toxicity study in the rat.

Developmental Toxicity Study in Rabbits (MRID 46203303)

Executive Summary: The petitioner has submitted 5 studies (MRIDs 46203303, 46203245, 46203246, 46203301, and 46203302) evaluating the effects of pinoxaden on developing rabbits. In the initial guideline developmental toxicity study (MRID 46203246), a dose of 100 mg/kg bw/day of pinoxaden administered by oral gavage was maternally toxic, and single fetal incidences (in separate litters) of defects of the diaphragm were observed. However, semen from a single buck had been used to inseminate all the dams whose offspring presented with these defects. Further, familial relationships of dams and bucks used in the study were not fully known. Therefore, two investigative non-guideline studies (MRIDs 46203301 and 46203302) were performed to investigate a possible parental etiology for the findings and to study the reproducibility of the outcome. Finally, a full repeat of the initial guideline study was performed using the whole range of original dose levels tested. This repeat study (MRID 46203303) is considered the definitive study and is presented in this risk assessment. All other supporting studies are summarized as Appendices at the end of this document.

In a developmental toxicity study (MRIDs 46203303, 46203245, 46203246, 46203301, 46203302, and 46203306), pinoxaden (97.2% a.i.; Batch # EZ005006) in 0.5% (w/w) carboxymethylcellulose + 0.1% (w/w) aqueous Tween 80 was administered daily by oral gavage at a dose volume of 4 mL/kg bw to 24 female Russian (Chbb:HM) rabbits/group at dose levels of 0, 3, 10, 30, or 100 mg/kg bw/day on gestation days (GD) 7 through 28. All does were killed on GD 29; their fetuses were removed by cesarean section and examined.

There were no effects of treatment on gross pathology.

Maternal toxicity was observed at 100 mg/kg/day. One doe was killed *in extremis* on GD 26 after exhibiting severe body-weight loss, recumbent position, and reduced activity during the 2 previous days. Additionally, 2 does were killed on GD 27 after showing signs of abortion.

At 100 mg/kg/day, when considering only females with viable fetuses, body-weight gains were decreased ($p \leq 0.05$) by 55% overall (GD 0-29) when uncorrected for gravid uterus weight. Additionally, uncorrected body-weight gains were decreased (not significant by 63% during treatment (GD 7-29). Gravid uterus weights were similar to controls. Food consumption was decreased ($p \leq 0.01$) by 47% during GD 7-12. When considering all pregnant females, body-weight gains were decreased ($p \leq 0.01$) by 84% during treatment and by 65% overall. Food consumption was decreased ($p \leq 0.05$) by 33-60% during GD 7-20.

The maternal LOAEL is 100 mg/kg bw/day, based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption. The maternal NOAEL is 30 mg/kg bw/day.

There were no treatment-related external, visceral, or skeletal malformations or variations. Fetal growth was unaffected by treatment.

At 100 mg/kg/day, 2 does were killed on GD 27 after showing signs of abortion, and 3 dead fetuses were observed. There were no premature deliveries. When considering all pregnant females, an increased ($p \leq 0.05$) number of does had complete early litter resorptions (7/24), causing increased ($p \leq 0.01$) total and early resorptions per doe and post-implantation loss, and decreased ($p \leq 0.01$) live litter size per doe. No effects of treatment were noted on live fetuses, late resorptions, or sex ratio. Therefore, the data were analyzed excluding these 7 does. When considering only females with viable fetuses, no effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), sex ratio, or post-implantation losses.

The developmental LOAEL is 100 mg/kg bw/day, based on increased incidence of complete early litter resorption. The developmental NOAEL is 30 mg/kg bw/day.

This study is classified **acceptable/guideline** (OPPTS 870.3700b) and satisfies the Guideline requirements for a developmental study in the rabbit.

Developmental Toxicity Study in Rabbits (MRID 46203303)

Original developmental toxicity study

This developmental toxicity study was intended to be the definitive study on the effects of NOA 407855 on development in the rabbit; however, interpretation of the data were problematic. Therefore, additional studies were planned. This study served as the range-finding study for the definitive developmental toxicity study (MRID 46203303). Only a summary is provided as requested by the Agency.

In a developmental toxicity study (MRID 46203246), NOA 407855 (Pinoxaden; 97.2% a.i.; Batch # EZ005006) in 0.5% (w/w) carboxymethylcellulose + 0.1% (w/w) aqueous Tween 80 was administered daily by oral gavage at a dose volume of 4 mL/kg bw to 24 female Russian (Chbb:HM) rabbits/group at dose levels of 0, 3, 10, 30, or 100 mg/kg bw/day on gestation days

(GD) 7 through 28. All does were killed on GD 29; their fetuses were removed by cesarean section and examined.

No effects of treatment were noted on survival, clinical signs, or gross pathology.

At 100 mg/kg bw/day, maternal body weights were decreased ($p \leq 0.05$) by 3-4% on GD 18-25. Body weight gains were decreased during treatment (GD 7-29) both uncorrected (↓68%; not significant [NS]) and corrected (↓71%; $p \leq 0.01$) for gravid uterus weight. Additionally, overall (GD 0-29) body weight gains were decreased by 63% (NS), and food consumption was decreased ($p \leq 0.05$) by 19-51% during treatment. Gravid uterus weights were similar to controls.

The maternal LOAEL is 100 mg/kg bw/day, based on decreased body weights, body weight gains, and food consumption. The maternal NOAEL is 30 mg/kg bw/day.

At 100 mg/kg bw/day, decreases ($p \leq 0.05$) were observed in fetal body weights for males (↓12%), females (↓13%), and both sexes (↓11%).

There were no abortions, premature deliveries, or complete litter losses. One dead fetus was observed in each of the 10 and 100 mg/kg bw/day groups. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early or late), or on sex ratio or post-implantation losses. No treatment-related external or skeletal findings were observed.

Diaphragmatic hernia, a malformation, was observed in the 30 (0.6% fetuses; 4.8% litters) and 100 (1.06% fetuses; 10.0% litters) mg/kg bw/day groups compared to 0 concurrent controls. The 100 mg/kg bw/day group was above the range of historical controls (0.0-0.9% fetuses; 0.0-5.9% litters). Fissure of the diaphragm, an anomaly, was also observed in one 100 mg/kg bw/day fetus (1.00% fetuses; 5.0% litters) compared to 0 concurrent and historical controls. Although these defects occurred in fetuses from different litters, it was observed that the affected does were artificially inseminated with semen from a single male rabbit. Therefore, an additional series of studies (MRIDs 46203301, 46203302, and 46203303) were planned to determine if the visceral defects were a result of treatment or associated with the parent animals.

The developmental LOAEL is 100 mg/kg bw/day based on decreased fetal body weights, and increased incidence of diaphragmatic hernia and fissure. The developmental NOAEL is 30 mg/kg bw/day.

This developmental toxicity study is classified as **acceptable/guideline**, and satisfies the Guideline requirements for a developmental toxicity study in the rabbit.

Developmental Toxicity Study in Rabbits (MRID 46203303)

Range-finding study for a developmental toxicity study

This range-finding study was performed to establish the dose levels used in the developmental toxicity study (MRID 46203246) summarized in Appendix 1. Only a summary is provided as requested by the Agency.

In a range-finding developmental toxicity study (MRID 46203245), NOA 407855 (Pinoxaden; 97.2% a.i.; Batch # EZ005006) in 0.5% (w/w) carboxymethylcellulose + 0.1% (w/w) aqueous Tween 80 was administered by oral gavage at a dose volume of 4 mL/kg to 8 female Russian (Chbb:HM) rabbits/group at nominal dose levels of 0, 30, 150, 300, 700, or 1000 mg/kg bw/day on gestation days (GD) 7-28. All does were killed on GD 29; their fetuses were removed by cesarean section and examined.

No effects of treatment were noted on gross pathology. Gravid uterus weights were comparable to controls.

At≥300 mg/kg bw/day, mortality and clinical signs of toxicity were observed. One 300 mg/kg bw/day female was found dead on GD 18, three 700 mg/kg bw/day females were found dead on GD 11-12, and two 1000 mg/kg bw/day females were found dead on GD 8-9. Hunched posture, reduced activity, and severe body weight loss were also observed. Therefore, surviving animals in these groups were killed for humane reasons prior to scheduled termination.

At 30 mg/kg bw/day, maternal body weight gains were decreased (not significant [NS]) by 21% during treatment (GD 7-29) and by 9% overall (GD 0-29). Food consumption was also decreased (NS) by 2-19% on GD 7-29.

At 150 mg/kg bw/day on GD 15, one doe was found in moribund condition and was killed for humane reasons, and one doe exhibited hunched posture and reduced activity. Body weights were generally decreased ($p \leq 0.05$) by 5-6% on GD 23-29. Body weight gains were decreased ($p \leq 0.01$) by 87% during treatment and by 68% overall. Food consumption was decreased (not significant [NS]) by 20-62% on GD 7-24 ($p \leq 0.01$ on GD 7-12).

The maternal LOAEL is 30 mg/kg bw/day, based on decreased body weight gains and food consumption. The maternal NOAEL was not observed.

At 150 mg/kg bw/day, decreases (NS) were observed in fetal body weights for males (↓12%), females (↓9%), and both sexes (↓12%). Additionally, 4/8 does had complete litter resorptions. Increased ($p \leq 0.05$) early resorptions per doe (4.9 treated vs 0.3 controls) and increased (NS) post-implantation loss (62.0% treated vs 7.3% controls) were observed.

There were no abortions or premature deliveries. One dead fetus was observed in the controls. No effects of treatment were noted on numbers of litters, live fetuses, late resorptions, or on sex ratio. No treatment-related external or visceral findings were observed.

The developmental LOAEL is 150 mg/kg bw/day based on decreased fetal body weights and increased early and complete litter resorptions. The developmental NOAEL is 30 mg/kg bw/day.

This range-finding developmental toxicity study is classified as **acceptable/non-guideline.**

Developmental Toxicity Study in Rabbits (MRID 46203303)

Non-standard developmental toxicity study using one male control

This developmental toxicity study was performed to clarify the potential association of a single buck in the occurrence of diaphragmatic defects observed in the fetuses of the initial developmental study (MRID 46203246) discussed in Appendix 1. Only a summary is provided as requested by the Agency.

In a non-guideline developmental toxicity study (MRID 46203302), NOA 407855 (Pinoxaden; 97.2% a.i.; Batch # EZ005006) in 0.5% (w/w) carboxymethylcellulose + 0.1% (w/w) aqueous Tween 80 was administered daily by oral gavage at a dose volume of 4 mL/kg bw to 24 female Russian (Chbb:HM) rabbits/group at dose levels of 0 or 100 mg/kg bw/day on gestation days (GD) 7 through 28. All does were killed on GD 29; their fetuses were removed by cesarean section and examined. All does were artificially inseminated with diluted semen from a single male. This male previously sired fetuses having defects of the diaphragm; however, since these fetuses were exposed to NOA 407855, it was unclear whether the defects were genetic in origin or treatment-related.

No effects of treatment were noted on survival or gross pathology.

At 100 mg/kg bw/day, piloerection was observed in one female beginning on GD 24. This animal was killed on GD 26 following abortion. Also, when considering only females with viable fetuses, maternal body weights were decreased ($p \leq 0.05$) by 5% on GD 21 and 24-29. Body weight gains were decreased ($p \leq 0.01$) during treatment (GD 7-29) both uncorrected (↓44%) and corrected (↓342%) for gravid uterus weight. Additionally, overall (GD 0-29) body weight gains were decreased ($p \leq 0.01$) by 34%, and food consumption was decreased ($p \leq 0.05$) by 17-32% during GD 7-20. Gravid uterus weights were similar to controls. Similar results were observed when calculations were performed on all pregnant females.

The maternal LOAEL is 100 mg/kg bw/day, based on decreased body weights, body weight gains, and food consumption. The maternal NOAEL was not observed.

There were no premature deliveries. At 100 mg/kg bw/day, 1 doe aborted on GD 26, and 2 dead fetus were observed. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early, late, or complete litter), or on sex ratio or post-implantation losses.

No treatment-related external or skeletal findings were observed. Spina bifida, a malformation, was observed in one 100 mg/kg bw/day fetus (1.47% fetuses; 5.9% litters) compared to 0 concurrent and historical controls. However, historical data provided by the breeder showed this defect does spontaneously occur in this breed of rabbit. Also at 100 mg/kg bw/day, enlarged gall bladder, a variation, was noted (13.65% fetuses; 29.4% litters) vs concurrent controls (2.46% fetuses; 15.8% litters), and enlarged stomach, a variation, was observed (0.84% fetuses; 5.9% litters) vs 0 concurrent controls. These findings were considered incidental. The occurrence of diaphragmatic hernia previously observed was not reproducible.

The developmental LOAEL was not observed. The developmental NOAEL is 100 mg/kg bw/day.

This developmental toxicity study is classified as **acceptable/non-guideline**.

Developmental Toxicity Study in Rabbits (MRID 46203303)

Non-standard developmental toxicity study using one male control

This developmental toxicity study was performed to clarify the potential association of a single buck in the occurrence of diaphragmatic defects observed in the fetuses of the initial developmental study (MRID 46203246) discussed in Appendix 1. Only a summary is provided as requested by the Agency.

In a non-guideline developmental toxicity study (MRID 46203301), NOA 407855 (Pinoxaden; 97.2% a.i.; Batch # EZ005006) in 0.5% (w/w) carboxymethylcellulose + 0.1% (w/w) aqueous Tween 80 was administered daily by oral gavage at a dose volume of 4 mL/kg bw to 24 female Russian (Chbb:HM) rabbits/group at dose levels of 0 or 100 mg/kg bw/day on gestation days (GD) 7 through 28. All does were killed on GD 29; their fetuses were removed by cesarean section and examined. All does were artificially inseminated with diluted semen from a total of 12 males; the male that previously sired fetuses having defects of the diaphragm was not used in this study.

No effects of treatment were noted on clinical signs or gross pathology.

At 100 mg/kg bw/day, 1 female was found dead on GD 23, and another was killed on GD 27 because of abortion. Also, when considering only females with viable fetuses, maternal body weights were decreased ($p \leq 0.05$) by 5% on GD 22-23, and 29. Body weight gains were decreased ($p \leq 0.05$) during treatment (GD 7-29) both uncorrected (↓35%) and corrected (↓171%) for gravid uterus weight. Additionally, overall (GD 0-29) body weight gains were decreased ($p \leq 0.05$) by 21%, and food consumption was decreased ($p \leq 0.01$) by 30% during GD 7-12. Gravid uterus weights were similar to controls. Similar results were observed when calculations were performed on all pregnant females.

The maternal LOAEL is 100 mg/kg bw/day, based on mortality, decreased body weights, body weight gains, and food consumption. The maternal NOAEL was not observed.

There were no premature deliveries or dead fetuses. At 100 mg/kg bw/day, 1 doe was killed on GD 27 following abortion, and 1 female was determined to have aborted at cesarean section. Additionally, when considering all pregnant females, 2 females had complete litter resorptions, and 19 early resorptions were observed, causing increased ($p \leq 0.05$) post-implantation losses (25.7% treated vs 3.4% controls). An increase ($p \leq 0.05$) in males per litter was noted (64.3%) compared to controls (40.9%). No effects of treatment were noted on numbers of litters, live fetuses, or late resorptions. When cesarean section data were examined for only females with viable fetuses, only the increased percentage of males per litter were observed.

No treatment-related external or skeletal findings were observed. At 100 mg/kg bw/day, a hindlimb position anomaly, a variation, was noted (2.27% fetuses; 9.1% litters), and enlarged gall bladder, a variation, was observed (1.52% fetuses; 9.1% litters), both vs 0 concurrent controls. Since each of these abnormalities were noted in single fetuses, these findings were considered incidental. The occurrence of diaphragmatic hernia previously observed was not reproducible.

The developmental LOAEL was not observed. The developmental NOAEL is 100 mg/kg bw/day.

This developmental toxicity study is classified as **acceptable/non-guideline**.

4.2.4 Reproductive Toxicity Study

Rat 2-Generation Reproduction Study (MRID 46203308)

Executive Summary: In a two-generation reproduction toxicity study (MRIDs 46203308 and 46203307), pinoxaden technical (97.2% a.i.; Batch # EZ005006) was administered daily by oral gavage in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80 at a dose volume of 10 mL/kg to Wistar (HanIbm: WIST) rats (30 animals/sex/dose) at dose levels of 0, 10, 50, 250 and 500 mg/kg bw/day. The P and F_1 parents were dosed for 10 weeks before they were mated to produce the F_1 and F_2 litters. The F_1 pups were weaned on postnatal day (PND) 22, and 30 pups/sex/group (1 pup/sex/litter as nearly as possible) were randomly selected as parents of the F_2 generation.

In the parental animals, no treatment-related effects were observed on survival, clinical signs, body-weight, overall body-weight gains, food consumption, estrous cycle length or periodicity, sperm measurements, numbers of ovarian follicles or corpora lutea, pre-coital interval, duration of gestation, or on mating, fertility, gestation, or parturition indices.

At 500 mg/kg bw/day, water consumption was increased ($p \leq 0.05$) throughout the study in the P and F_1 males (incr. 23-82%), and during pre-mating in the females (incr. 16-67%). Increases ($p \leq 0.01$) were observed in absolute and relative (to body) kidney weights in the P (incr. 13-21%) and F_1 (incr. 10-16%) males. Increased incidences of the following were observed compared to controls: I) renal pelvic dilatation at necropsy in the P males; ii) slight to marked dilatation of the renal pelvis during microscopic pathology in the P males; iii) minimal to moderate renal tubular atrophy in the P and F_1 males; iv) chronic nephropathy in the P and F_1 males; v) minimal to moderate renal tubular atrophy in the P females; and vi) minimal to moderate chronic nephropathy in the P and F_1 females.

The LOAEL for parental toxicity is 500 mg/kg bw/day, based on increased water consumption, renal tubular atrophy, and chronic nephropathy in both sexes, and increased incidence of renal pelvic dilatation in the males. The NOAEL is 250 mg/kg bw/day.

In the offspring, no treatment-related effects were observed on post-implantation survival, live birth, viability, or lactation indices, on the sex ratio, clinical signs, sexual maturation, organ weights, gross pathology, or microscopic pathology.

At 500 mg/kg bw/day, in the F_1 pups, body-weights were decreased ($p \leq 0.05$) on PND 7-21 in the males (decreased 7-10%), and on PND 4-21 in the females (decreased 7-11%). Overall (PND 0-21) body-weight gains were also decreased ($p \leq 0.01$) in both sexes (decreased 7-8%). In the F_2 males, body-weights were decreased ($p \leq 0.05$) on PND 7-14 (decreased 6-7%).

The LOAEL for offspring toxicity is 500 mg/kg bw/day, based on decreased body-weights and body-weight gains in the F_1 pups, and decreased body-weights in the F_2 males. The NOAEL is 250 mg/kg bw/day.

The LOAEL for reproductive performance was not observed. The NOAEL for reproductive performance is 500 mg/kg bw/day.

This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

4.2.5 Additional Information from Literature Sources

There is no additional information on the toxicity of pinoxaden that is currently available in the literature as demonstrated by a TOXNET search of 3/24/2005.

4.2.6 Pre-and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

There is no evidence of qualitative and/or qualitative evidence of increased susceptibility of rat and rabbit fetuses to *in utero* exposure to pinoxaden. There is no evidence of increased qualitative and/or quantitative evidence of increased susceptibility to pinoxaden following pre-natal exposure in a 2-generation reproduction study in rats.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

No evidence of increased susceptibility to pinoxaden following pre-natal exposure in a 2-generation reproduction study in rats. There are no concerns or residual uncertainties for pre-/post-natal toxicity.

4.3 Recommendation for a Developmental Neurotoxicity Study

There is no concern for neurotoxicity resulting from exposure to pinoxaden. The clinical signs (hunched postured, piloerection, decreased activity, cold to touch) observed in rats and dogs were at very high dose levels and are sometimes exhibited in compromised animals. Other signs indicative of neurotoxicity, i.e. ataxia, tremors, tilting head, convulsions or altered gait (i.e., staggered gait or circling) were not observed in these or in other studies with pinoxaden. Neurotoxicity was not observed in the acute (MRID 46203331) and subchronic (MRID 46203332) rat neurotoxicity studies. No indication of abnormalities in the development of the fetal nervous system was observed in the prenatal developmental toxicity studies in either rats or rabbits at dose levels up to 800 and 100 mg/kg/day, respectively. No evidence of neuropathology was observed in the database.

Therefore, a developmental neurotoxicity study in rats is not required.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: Developmental Toxicity - Rabbit § OPPTS 870.3700

MRID No.: 46203303

Executive Summary: See Section 4.2.3 (second study).

Dose and Endpoint for Establishing an aRfD: Developmental NOAEL = 30 mg/kg/day, based on increased incidence of complete early litter resorption at the LOAEL of 100 mg/kg/day.

UF: 100 (10x for interspecies extrapolation and 10x for intraspecies variations)

Comments about Study/Endpoint and Uncertainty Factor: This study provides the lowest dose attributable to a single-dose developmental effect (increased incidence of early resorptions) applicable to the female 13-49 years of age.

$$\textbf{Acute RfD} = \frac{30 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.3 \text{ mg/kg/day}$$

4.4.2 Acute Reference Dose (aRfD) - General Population

An endpoint of concern attributable to a single dose effect was not identified in the database. Decreased body weights and body weight gains were seen during gestation days 7-12 in the developmental toxicity study in rabbits; these effects were considered marginal. Therefore, this study and endpoint were not used for this risk assessment. Quantification of acute risk to general population including infants and children is not required.

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Developmental Toxicity - Rabbit § OPPTS 870.3700

MRID No.: 46203303

Executive Summary: See Section 4.2.3 (second study)

Dose and Endpoint for Establishing a cRfD: Maternal NOAEL = 30 mg/kg/day, based on morbid condition in one rabbit (mortality), abortion, decreased body weights, body weight gains and food consumption seen at the LOAEL of 100 mg/kg/day.

UF: 100 (10x for interspecies extrapolation and 10x for intraspecies variations)

Comments about Study/Endpoint and Uncertainty Factor: This study provides the lowest NOAEL in the database for chronic effects such as decreases in body weights and body weight gains.

Chronic RfD = $\frac{\text{30 mg/kg (NOAEL)}}{\text{100 (UF)}}$ = 0.3 mg/kg/day

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Study Selected: Developmental Toxicity - Rabbit § OPPTS 870.3700

MRID No.: 46203303

Executive Summary: See Section 4.2.3 (second study)

Dose and Endpoint: Maternal NOAEL = 30 mg/kg/day, based on morbid condition in one rabbit (mortality), abortion, decreased body weights, body weight gains and food consumption seen at the LOAEL of 100 mg/kg/day.

Comments about Study/Endpoint: This endpoint would be appropriate for the route, duration of exposure (1-30 days; 1 - 6 months) and population of concern (infants and children), if residential uses were added to the use pattern. This study provides lowest NOAEL in the database.

4.4.5 Dermal Absorption

Dermal Absorption Factor: 40%

Dermal absorption is estimated to be 40% based on the results of the *in vivo/in vitro* dermal penetration study in rats using the EC 100 formulation. (The emulsifiable concentrate (EC) formulation will be used in the field and is believed to be much more absorbable than technical pinoxaden without the emulsifiers.) In this study with the EC formulation, 36% of the dose applied to the skin of rats in an in vivo study was absorbed over the following day (24 hours post-exposure). Absorption of the EC formulation from excised rat skin in an in vitro study was 65.5% of the applied dose after 24 hours post-exposure. For excised human skin, absorption of radioactivity was minimal regardless of the dosing vehicle and dose level in an in vitro study. Absorption accounted 0.36-1.84% of the applied dose after a 24-hour exposure at doses from 5-400 $\mu g/cm^2$. Thus, in the *in vitro* studies, absorption was considerably higher in rat skin than in human skin. Additionally, absorption of the test substance in the *in vivo* rat study was comparable to the absorption in the *in vitro* study with rat skin. Therefore, the data suggest that *in vivo* absorption in humans would be considerably lower than in the rat.

4.4.6 Dermal Exposure (Short, Intermediate and Long Term)

Study Selected: Developmental Toxicity - Rabbit § OPPTS 870.3700

MRID No.: 46203303

Executive Summary: See Section 4.2.3 (second study)

Dose and Endpoint: Maternal NOAEL = 30 mg/kg/day, based on morbid condition in one rabbit (mortality), abortion, decreased body weights, body weight gains and food consumption seen at the LOAEL of 100 mg/kg/day.

UF: 100 (10x for interspecies extrapolation and 10x for intraspecies variations)

Comments about Study/Endpoint: No toxicity was seen in a 28-day dermal toxicity study in rats, however, this study was not selected because this study does not measure skeletal variations seen in the developmental study that occurred at lower doses when using a 40% dermal-absorption factor.

4.4.7 Inhalation Exposure (Short, Intermediate and Long Term)

Study Selected: Developmental Toxicity - Rabbit § OPPTS 870.3700

MRID No.: 46203303

Executive Summary: See Section 4.2.3 (second study)

Dose and Endpoint: Maternal NOAEL = 30 mg/kg/day, based on morbid condition in one rabbit (mortality), abortion, decreased body weights, body weight gains and food consumption seen at the LOAEL of 100 mg/kg/day.

Comments about Study/Endpoint: This study provides lowest NOAEL in the database. No inhalation study is available in the database.

4.4.8 Margins of Exposure

The target Margins of Exposure (MOEs) for occupational exposure risk assessments are as follows:

Route / Duration	Short-Term (1-30 days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	N/A		
Dermal			
Inhalation			

For Occupational exposure: This is based on the conventional uncertainty factor of 100X (10X for intraspecies variation and 10X for interspecies extrapolation).

For Residential exposure: Not applicable, since there are no residential uses.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

No residential uses are proposed for pinoxaden at this time. Therefore, aggregate risk consists of exposure from food and drinking water sources only. Acute and chronic aggregate risks were assessed.

To better evaluate aggregate risk associated with exposure through food and drinking water, OPP is no longer comparing Estimated Drinking Water Concentration (EDWCs) generated by water quality models with Drinking Water Levels of Comparison (DWLOC) . Instead, OPP is now directly incorporating the actual water quality model output concentrations into the risk assessment. This method of incorporating water concentrations into our aggregate assessments relies on actual CSFII-reported drinking water consumptions and more appropriately reflects the full distribution of drinking water concentrations.

4.4.10 Classification of Carcinogenic Potential

The Cancer Assessment Review Committee (CARC) concluded that the submitted studies are inadequate to evaluate carcinogenic potential of pinoxaden due to the absence of an acceptable mouse carcinogenicity study. In accordance with the EPA Guidelines for Carcinogen Risk Assessment (March, 2005), the Committee classified pinoxaden into the category **"Data Are Inadequate for An Assessment of Human Carcinogenic Potential".**

Table 4.4 Summary of Toxicological Doses and Endpoints for Pinoxaden for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	NOAEL = 30 mg/kg/day UF = 100 Acute RfD = 0.30 mg/kg	FQPA SF - 1X aPAD = 0.30 mg/kg	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on increased incidence of complete early litter resorption
Acute Dietary (general population)	N/A	N/A	An endpoint of concern attributable to a single dose effect was not identified in the database. Quantification of acute risk to general population including infants and children is not required.
Chronic Dietary (all populations)	NOAEL = 30 mg/kg/day UF = 100 Chronic RfD = 0.30 mg/kg/day	FQPA SF - 1X cPAD = 0.30 mg/kg/day	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Incidental Oral Short-Term (1 - 30 days)	NOAEL = 30 mg/kg/day	LOC = MOE - 100 (residential includes the FQPA SF)	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF)	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Dermal Short-Term (1 - 30 days)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF) LOC for occupational =100 Dermal-absorption rate=40%	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Intermediate-Term (1 - 6 months)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF) LOC = MOE=100 (Occupational) Dermal-absorption rate=40%	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Dermal Long-Term (> 6 months)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF) LOC = MOE=100 (Occupational) Dermal-absorption rate=40%	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Inhalation Short-Term (1 - 30 days)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF) LOC = MOE=100 (Occupational) Inhalation-absorption rate=100%	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Inhalation Intermediate-Term (1 - 6 months)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF) LOC = MOE=100 (Occupational) Inhalation-absorption rate=100%	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Inhalation Long-Term (> 6 months)	NOAEL = 30 mg/kg/day	LOC = MOE=100 (residential includes the FQPA SF) LOC = MOE=100 (Occupational) Inhalation-absorption rate=100%	Developmental toxicity - rabbit LOAEL = 100 mg/kg/day based on morbid condition in one rabbit (mortality), clinical signs of toxicity in a morbid rabbit, abortion, decreased body weights, body weight gains and food consumption.
Cancer (oral, dermal, inhalation)	**Classification:** Data Are Inadequate for An Assessment of Human Carcinogenic Potential		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse-effect level, LOAEL = lowest observed adverse-effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* Refer to Section 4.5

4.5 Special FQPA Safety Factor

Based on the hazard characterization data, the pinoxaden risk assessment team recommended the special FQPA SF be reduced to 1x because there are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. The pinoxaden risk assessment team evaluated the quality of the exposure data and based on these data, recommended that the special FQPA SF be reduced to 1x. This recommendation is based on the following:

- The dietary exposure assessment utilizes proposed tolerance level residues and 100% crop treated information for all commodities. By using these screening-level assessments, chronic exposures/risks will not be underestimated.

- The dietary drinking water assessment utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

- There are no residential uses proposed for pinoxaden at this time.

4.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on pinoxaden, there was no estrogen, androgen, and/or thyroid mediated toxicity.

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, pinoxaden may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

Pinoxaden is a new active ingredient. Therefore, public health information is not available.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

The nature of the residue in wheat and livestock is adequately understood for the petitioned use based on acceptable metabolism studies conducted on wheat, lactating goats, and laying hens. In both wheat and livestock, pinoxaden undergoes hydrolysis of the ester moiety, hydroxylation and conjugation with sugars. In most of the metabolites identified, the three-ring backbone of pinoxaden remains intact. However, some of the metabolites identified in wheat are different than those in livestock metabolism studies. The residues of concern for the purpose of tolerance enforcement and risk assessment for wheat, barley and poultry are pinoxaden and its metabolites M2, M4 (free and conjugated), and M6; and for ruminants are pinoxaden and its metabolites M2 and M4 (free and conjugated). The residues of concern for rotational crops are pinoxaden, M2, M3 (free and conjugate), M10, and M11.

Combined residues of pinoxaden and M2 (as M2), and residues of M4 and M6 were quantitated by adequately-validated high-performance liquid chromatography (HPLC)/tandem mass spectrometry (MS/MS). The proposed enforcement methodology for plants needs to pass a petition method validation (PMV) by the Analytical Chemistry Laboratory/Biological and Economics Analysis Division (ACL/BEAD) before the method can be deemed adequate for tolerance enforcement. The proposed enforcement methodology for livestock is not currently adequate because it was not validated for residues of pinoxaden and M2. Based on its similarities to the plant enforcement method, HED expects that the proposed livestock method will be adequate for quantification of pinoxaden and M2. **Submission of the validation data for pinoxaden and M2 may thus be a condition of registration.**

The petitioner submitted magnitude of the residue data for wheat and barley. The field trial studies were conducted using the proposed application scenarios and in the regions suggested in OPPTS 860.1500 for establishment of a tolerance in/on the crops requested. The petitioner also submitted the required processing studies for the proposed crops. The field trial and processing residue data were generated using adequately-validated analytical methods (storage intervals have also been validated). Based on the field trial and processing studies, HED concludes that the tolerances listed in the recommendation section are appropriate. A revised Section F is requested; no additional field trial or processing data are necessary.

The petitioner submitted feeding studies on ruminant and poultry. Although the residues were <LOQ, tolerances are still required since the studies were not conducted at ≥10X. Since the livestock tissues were not analyzed for pinoxaden and M2, those residues were conservatively estimated to be at LOQ (based on plant and livestock metabolism studies) in calculation of maximum combined residues for tolerance setting.

The submitted storage stability studies support the storage intervals and conditions of M4 and M6 in livestock commodities and that of M2, M4, and M6 in whole wheat, straw and grain. Although, pinoxaden and M2 were not included in livestock storage stability study, since the levels of those analytes in the ruminant tissues are not expected to exceed LOQ (based on plant and livestock metabolism studies), and that the M4 is the major residue in feed items, no further storage stability data are required for livestock samples. However, a study demonstrating the storage stability of M2, M4 and M6 in wheat-processed fractions (aspirated grain fractions (AGF), bran, flour, middling, shorts and germ) for a minimum duration of 6 month is required.

The petitioner submitted confined rotational crop studies for spring and winter wheat, head lettuce, mustard greens, radish and turnip under various plant-back intervals (PBIs). M3, M10, and M11 were >0.01 ppm in rotated spring wheat forage and fodder with 15-day and/or 30-day PBIs; thus, M3, M10, and M11 (in addition to the parent and M2) were determined to be residues of concern. At the 29- or 30-day PBI, none of the metabolites identified (M2, M3, M8, M9, M10, M11 & M32) were quantitated at levels greater that 0.01 ppm, except M3 in spring wheat forage; at the 120-day PBI, all the identified metabolites were quantitated at levels lower than 0.01 ppm in spring wheat forage. **Therefore, the proposed PBIs should be amended to limit the 30-day PBI to leafy and root crops only and also to add a 120-day PBI for other cereal grains (besides wheat and barley) and all other crops (besides leafy and root crops).** Pinoxaden was not detected in any rotated crop matrices at any PBIs (from 15 to 365 days) since it was hydrolyzed rapidly (disappeared by day 3) in soil yielding M2. M2 was further hydroxylated forming M3 which was taken up from the soil by the rotated crops.

Provided a revised Section F is submitted, and the Agency validations of the proposed analytical enforcement methods are successful, HED concludes there are no residue chemistry toxicology or occupational/residential exposure data requirements that would preclude the establishment of a **conditional** registration and the following permanent tolerances:

1) For the combined residues of pinoxaden, and its metabolites M2, free and conjugated forms of M4, and M6, calculated as pinoxaden, in/on the following commodities:

Wheat, grain	1.3 ppm
Wheat, forage	3.5 ppm
Wheat, hay	2.0 ppm
Wheat, bran	3.0 ppm
Wheat, straw	1.5 ppm
Barley, grain	0.9 ppm
Barley, hay	1.5 ppm
Barley, straw	1.0 ppm
Barley, bran	1.6 ppm
Egg	0.06 ppm
Poultry, fat	0.06 ppm
Poultry, meat	0.06 ppm
Poultry, meat byproduct	0.06 ppm

2) For the combined residues of **pinoxaden**, and its metabolites **M2**, and free and conjugated forms of **M4**, calculated as pinoxaden, in/on the following commodities:

Milk	0.02 ppm
Cattle[1], fat	0.04 ppm
Cattle[1], meat	0.04 ppm
Cattle[1], meat by product	0.04 ppm

1. Includes sheep, horse, goat and hog.

HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following residue chemistry data:

- Additional storage stability data for wheat and barley processed fractions.
- Additional validation data for pinoxaden and M2 residues in livestock commodities (ruminant and poultry).

6.1.2 Acute and Chronic Dietary Exposure and Risk

Residues of Concern:
The residues of concern for the purpose of tolerance enforcement and risk assessment for wheat and barley and poultry are pinoxaden and its metabolites M2, M4 (free and conjugated), and M6; and for ruminants are pinoxaden and its metabolites M2 and M4 (free and conjugated). The residues of concern for rotational crops are pinoxaden, M2, M3 (free and conjugate), M10, and M11.

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.0) which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Drinking water was directly incorporated into the dietary analyses.

Acute Dietary Exposure Results and Characterization

The Tier 1 acute analysis for females 13-49 years old assumed 100% crop treated, DEEM 7.81 default processing factors and tolerance-level residues. Drinking water was incorporated directly into the dietary assessment using the annual peak concentration for surface water generated by the PRZM -EXAMS model as a high-end estimate (0.00076 ppm; 90th percentile annual daily maximum).

The resulting risk estimates for females 13-49 years old is 1.5% of the aPAD at the 95th percentile.

Since drinking water was included directly into the acute dietary analysis, the risk estimate represents acute aggregate risk from pinoxaden.

Chronic Dietary Exposure Results and Characterization

The Tier 1 chronic analysis assumed 100% crop treated, DEEM 7.81 default processing factors and tolerance-level residues. Drinking water was incorporated directly into the dietary assessment using the annual mean concentration for surface water generated by the PRZM-EXAMS model as a high-end estimate (0.000473 ppm; 90th percentile annual mean).

The chronic dietary exposure estimate for the general population is 0.9% of the cPAD. The estimate for the highest exposed population subgroup (children 1-2 years old) is 2.1% of the cPAD.

Since drinking water was included directly into the chronic dietary analysis, the risk estimate represents chronic aggregate risk from pinoxaden.

A cancer dietary risk assessment was not performed since CARC concluded that "Data Are Inadequate for An Assessment of Human Carcinogenic Potential."

Table 6.1.2. Summary of Dietary Exposure and Risk for Pinoxaden Including Drinking Water

Population Subgroup	Acute Dietary [1]		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	N/A		0.0026	0.9
All Infants (< 1 year old)			0.0014	0.5
Females 13-49 years old	0.0046	1.5	0.002	0.7
Children 1-2 years old	N/A		0.0063	2.1
Children 3-5 years old			0.0061	2.0
Children 6-12 years old			0.0042	1.4
Youth 13-19 years old			0.0025	0.8
Adults 20-49 years old			0.0021	0.7
Adults 50+ years old			0.00059	0.2

1. Acute dietary exposure is from 95th percentile of exposure distribution.

These acute and chronic dietary exposure and risk estimates are conservative since they assumed 100% crop treated, DEEM 7.81 default processing factors and tolerance-level residues and were based on screening-level estimates of drinking water concentrations generated by the PRZM-EXAMS models. They could be further refined through the use of anticipated residues, empirical processing factors and percent crop treated data, as well as refined drinking water estimates.

6.2 Water Exposure/Risk Pathway

Hydrolysis of pinoxaden is pH dependent and faster under basic conditions. Aqueous photolysis of pinoxaden is not a major dissipation route when exposed to sunlight. In soil, photolysis is also not a significant pathway for degradation for pinoxaden without hydrolytic degradation.

Acceptable laboratory studies showed that pinoxaden degrades rapidly under aerobic soil metabolism conditions with half-lives ranges from 2-3 days forming the major degradate M2,

which degrades further to form the degradate M3.

Volatility is not a significant route of dissipation. The major degradates (M2 and M3) are considered to be mobile based on Freundlich K_{ads} values ranging from 0.06-128 ml/g, and 0856-0.28 ml/g, respectively, in three test soils (loamy sand, loam, silty clay loam textures).

EFED currently has no monitoring data for pinoxaden in surface or groundwater.

Surface Water
EFED has conducted a Tier II drinking water assessment for pinoxaden and its major transformation products, M2 and M3, using the Tier II screening models PRZM[1] and EXAMS[2] with the Index Reservoir and Percent Crop Area adjustment (IR-PCA PRZM/EXAMS). The surface water concentrations of pinoxaden were modeled based on its use on wheat in North Dakota (aerial application) at the maximum application rate of 0.0624 lb ai/acre. According to U.S.D.A., in 2004, North Dakota's wheat production is ranked second in the Nation, behind Kansas. The half-lives were calculated based on the summation of toxic pinoxaden residues.

The Index Reservoir represents a potentially vulnerable drinking water source based on the geometry of an actual reservoir and its watershed in a specific area (Illinois), using regional specific cropping patterns, weather, soils, and other factors.

The PCA is a generic watershed-based adjustment factor which represents the portion of a watershed planted to a crop or crops. The PCA will be applied to pesticide concentrations estimated for the surface water component of the drinking water exposure assessment using PRZM/EXAMS with the Index Reservoir scenario.

The IR-PCA PRZM/EXAMS modeling results indicate that pinoxaden has the potential to contaminate surface waters by spray drift, and runoff in areas with large amounts of annual rainfall.

Groundwater
No monitoring data are available with which to estimate concentrations of pinoxaden in groundwater at the present time. Therefore, the SCI-GROW model was used to estimate potential groundwater concentrations of pinoxaden and its degradates M2 and M3.

Groundwater EECs predicted using the SCI-GROW screening model are substantially less (0.13 ppb) than those estimated for surface water using PRZM and EXAMS. However, the major degradate M2 should persist longer in groundwater than in surface water.

Table 6.2 Estimated environmental concentrations in surface and groundwater for pinoxaden and its major degradates, M2 and M3 from use on wheat.

	model EDWCs (µg/L)
	Aerial Application
Surface water/ peak (90th percentile annual daily max.)	0.76
Surface water/ 90th percentile annual mean)	0.47
Surface water/ 36-year overall mean	0.32
Groundwater	0.13

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on applying a percent crop area Adjustment to Tier 2 Surface Water Model Estimates for Pesticide Drinking Water Exposure Assessments. 12-07-99; maximum application rate of 0.0624 lb ai/A, mean K_{ads} = 4.2 mL/g, aerobic soil metabolism half-life of 29.4 days.

[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.0624 lb ai/A, a median K_{oc} of 4.2, and a aerobic soil metabolism half-life of 29.4 days.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

There are no proposed or existing residential uses of pinoxaden.

6.3.1 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for pinoxaden. HED has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, HED is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. HED has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, HED may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For pinoxaden, no residential uses are proposed. Therefore, aggregate risk will consist of exposure from food and drinking water sources. Acute and chronic aggregate risks were calculated.

To better evaluate aggregate risk associated with exposure through food and drinking water, OPP is no longer comparing Estimated Drinking Water Concentration (EDWCs) generated by water quality models with Drinking Water Levels of Comparison (DWLOC) . Instead, OPP is now directly incorporating the actual water quality model output concentrations into the risk assessment. This method of incorporating water concentrations into our aggregate assessments relies on actual CSFII-reported drinking water consumptions and more appropriately reflects the full distribution of drinking water concentrations.

7.1 Acute Aggregate Risk

To assess acute aggregate risk, HED incorporated drinking water estimates directly into the dietary analysis. Results are reported in Table 6.1.2.

An endpoint of concern attributable to a single dose effect was not identified in the database for the general population. Quantification of acute risk to general population including infants and children is not required.

The Tier 1 acute analysis for females 13-49 years old assumed 100% crop treated, DEEM 7.81 default processing factors (when empirical data were not available) and tolerance-level residues. Drinking water was incorporated directly into the dietary assessment using the annual peak concentration for surface water generated by the PRZM -EXAMS model as a high-end estimate (0.00076 ppm; 90th percentile annual daily maximum).

The resulting acute dietary risk estimate for females 13-49 years old is 1.5 % of the aPAD at the 95th percentile.

7.2 Short-Term Aggregate Risk

Since there are no existing or proposed residential uses for pinoxaden, short-term aggregate risk was not calculated.

7.3 Intermediate-Term Aggregate Risk

Since there are no existing or proposed residential uses for pinoxaden, intermediate-term aggregate risk was not calculated.

7.4 Long-Term (Chronic) Aggregate Risk

To assess chronic aggregate risk, HED incorporated drinking water estimates directly into the dietary analysis. Results are reported in Table 6.1.2.

The Tier 1 chronic analysis assumed 100% crop treated, DEEM 7.81 default processing factors (when empirical data were not available) and tolerance-level residues. Drinking water was incorporated directly into the dietary assessment using the annual mean concentration for surface water generated by the PRZM-EXAMS model as a high-end estimate (0.000473 ppm; 90th percentile annual mean).

The chronic dietary exposure estimate for the general population is 0.9% of the cPAD. The estimate for the highest exposed population subgroup (children 1-2 years old) is 2.1% of the cPAD.

7.5 Aggregate Cancer Risk

The CARC concluded that data are inadequate for an assessment of human carcinogenic potential due to the absence of an acceptable mouse carcinogenicity study. Based on the weight of the evidence, HED believes that pinoxaden is not likely to pose a cancer risk. Therefore, an aggregate cancer risk assessment was not performed.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for pinoxaden and any other substances, and pinoxaden does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that pinoxaden has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

9.1 Short-/Intermediate-/Long-Term Handler Risk

Based upon the proposed use pattern, HED believes the most highly-exposed occupational pesticide handlers (i.e., mixers, loaders, applicators) are:
1) Mixer/loader using open-pour loading of liquids in support of aerial operations
2) Applicator using open-cab ground-boom equipment
3) Aerial applicator (pilot)

Applicators using open-cab ground equipment typically experience greater exposures than aerial applicators however the estimated exposure for an aerial applicator is presented. HED expects that most occupational handler exposures will be short-term in duration (1 - 30 days). The ExpoSAC maintains that it is possible for a commercial applicator to be exposed to intermediate-term exposures (1 - 6 months) by treating farm after farm for the same pest complex, however, HED believes that the probability for intermediate-term exposures is very low. Since the doses

and endpoints for short- and intermediate-term risk assessment are the same, risks calculated below represent both exposure durations.

It is expected that some private (i.e., grower) applicators may perform all tasks, that is, mix, load and apply the material. However, HED ExpoSAC draft Standard Operating Procedure (SOP) (29 March 2000) directs that although the same individual may perform all tasks, in some cases they shall be assessed separately.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand-held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of PPE for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as with a single layer of work clothing and the use of protective gloves or other PPE as might be necessary.

Short- and intermediate-term handler risks were estimated. A dermal-absorption factor of 40% was use to calculate occupational risks. HED assumed 100% inhalation absorption. The level of concern for occupational pesticide handlers and agricultural workers is a MOE of at least 100.

Table 9.1 Estimated Handler Exposure and Risk from the Use of Pinoxaden on Wheat and Barley

Unit Exposure[1] mg a.i./lb handled	Applic. Rate[2]	Units Treated[3] Per Day	Average Daily Dose[4] mg a.i./kg bw/day	NOAEL[5] mg a.i./kg bw/day	MOE[6]
Mixer/Loader -Liquid - Open-pour - Supporting Aerial Operations					
Dermal: No Gloves 2.9 HC With Gloves 0.023 HC Inhal. 0.0012 MC	0.062 lb a.i./A	1200 A	Dermal: No Gloves 1.2 With Gloves 0.0098 Inhal 0.0013	30	No Gloves 24 With Gloves 2,700
Applicator - Ground-boom - Open Cab					
Dermal: No Gloves 0.014 HC With Gloves 0.014 MC Inhal 0.00074 HC	0.062 lb a.i./A	200 A	Dermal: No Gloves 0.001 With Gloves 0.001 Inhal 0.00013	30	No Gloves 27,000 With Gloves 27,000
Aerial Applicator (pilots not required to wear gloves)					
Dermal: No Gloves 0.0022 MC Inhal. 0.000068 MC	0. 0623 lb a.i./A	1200 A	Dermal: No Gloves 0.00094 Inhal 0.000073	30	No Gloves 30,000

1. Unit Exposures are taken from "PHED Surrogate Exposure Guide", Estimates of Worker Exposure from PHED, v. 1.1, August, 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from proposed label.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1, Science Advisory Council for Exposure; Revised 5 July 2000;
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated * absorption factor (40 % dermal; 100 % inhalation ÷ Body-weight (70 kg since NOAELs are identified from a developmental study with maternal effects).
5. NOAEL = 30 mg a.i./kg bw/day
6. MOE = NOAEL ÷ ADD. Short-term dermal and short-term inhalation exposures are summed and divided into the NOAEL. The dermal and inhalation endpoints are the same, are identified from the same study and have the same NOAELs for all exposure durations.

Provided that mixer/loaders use protective gloves as specified on the proposed label, all MOEs are greater than 100 and therefore do not exceed HED's level of concern.

9.2 Short/Intermediate/Long-Term Postapplication Risk

There is a potential for post-application exposure of agricultural workers to pesticides during the course of typical agricultural activities. HED in conjunction with the ARTF has identified a number of post-application agricultural activities that may occur. HED has also identified TCs (cm^2/hr) relative to the various activities which expresses the amount of foliar contact over time, during each of the activities. The highest (i.e., most conservative) TC relative to the early, post-emergence treatment of wheat is for scouting with a TC of 100 cm^2/hr. Post-application exposure is herein assessed using the highest proposed rate of application and a TC of 100 cm^2/hr.

The TCs used in this assessment are from an interim TC SOP developed by the ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of the ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural

practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to HED, and from studies in the published scientific literature.

Lacking compound-specific DFR data, HED assumes 20% of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR $\mu g/cm^2$ * TC cm^2/hr * hr/day * 0.001 mg/μg * 1/70 kg bw

and where:

Surrogate Dislodgeable Foliar Residue (DFR) = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54 x 10^8 $\mu g/lb$ * 2.47 x 10^{-8} A/cm^2.

TC =100 cm^2/hr

$\therefore$ DFR = 0.062 lb a.i./A * 0.20 * $(1\text{-}0)^0$ * 4.54E8 μg a.i./lb * 2.47E-8A/cm^2 = 0.14 $\mu g/cm^2$

PDR = 0.14 $\mu g/cm^2$ * 0.001 mg/μg * 100 cm^2/hr * 8 hr/day = 0.112 mg a.i./day * 0.40 (dermal-absorption rate) $\div$ 70 kg bw = 0.00064 mg a.i./kg bw/day

MOE = NOAEL $\div$ PDR

$\therefore$ 30 mg a.i./kg bw/day $\div$ 0.00064 mg a.i./kg bw/day = 47,000

This estimate is considered to be a screening-level estimate (i.e., conservative, protective). HED's level of concern for occupational risk is a MOE of at least 100. In this case, the MOE is greater than 100. Therefore, short-term, intermediate-term or long-term duration post-application dermal risks are not of concern for agricultural workers. Post-application inhalation exposure is expected to be negligible.

9.3 Occupational Handler and Postapplication Cancer Risk

The CARC concluded that data are inadequate for an assessment of human carcinogenic potential due to the absence of an acceptable mouse carcinogenicity study. Based on the weight of the evidence, HED believes that pinoxaden is not likely to pose a cancer risk. Therefore, an aggregate cancer risk assessment was not performed.

Restricted-Entry Level (REI)

The proposed label lists a 48 hour REI. Pinoxaden is classified in Acute Toxicity Category III for acute dermal toxicity. It is classified in Category IV for acute inhalation toxicity and primary skin irritation. It is not a dermal sensitizer. It is classified in Acute Toxicity Category I for primary eye irritation. Therefore, the proposed REI is in compliance with the interim worker

protection standard (WPS) restricted entry interval and should be protective of agricultural workers re-entering treated crop sites.

10.0 Data Needs and Label Requirements

Toxicology - none.
Occupational Exposure - none.

Residue Chemistry

860.1200 Proposed Use

The label should be amended to include the following PBIs:

0-day ..... PBI for wheat & barley
30-day PBI ..... for leafy & root crops
120-day PBI ..... for other cereal grains and all other crops

860.1340 Residue Analytical Methods

Plant Commodity Method

The proposed plant enforcement methods need to pass a PMV by Agency chemists at ACL/BEAD before the method can be deemed adequate for tolerance enforcement. Method 117-01 has been forwarded to ACL/BEAD for the PMV (DP# 313799, M. Sahafeyan, 3/10/05).

Livestock Commodity Methods

The proposed enforcement method for livestock commodities (Method T001530-03) is inadequate since it only analyzes for M4 and M6 metabolites and does not analyze for all the metabolites of concern in ruminants (pinoxaden as M2, M2, and M4) and poultry (pinoxaden as M2, M2, M4, and M6). Additional validation data for pinoxaden and M2 residues in livestock commodities (ruminant and poultry) should be submitted.

860.1380 Storage Stability

The freezer storage stability of the metabolites M2, M4 and M6 was not demonstrated in barley and wheat processed fractions. A study demonstrating the storage stability of M2, M4 and M6 in barley processed fractions (bran, flour and pearled barley) for a minimum duration of 15 month is requested. A study demonstrating the storage stability of M2, M4 and M6 in wheat processed fractions (AGF, bran, flour, middling, shorts and germ) for a minimum duration of 6 month is requested.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F as specified in the recommendation section.

Note to RD: The preferred chemical name for pinoxaden is "8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7*H*-pyrazolo[1,2-*d*][1,4,5] oxadiazepin-9-yl 2,2-dimethylpropanoate."

Tolerances are also required on meat, milk, poultry and egg (MMPE) .

References

CARC Report:	*Pinoxaden: Report of the Cancer Assessment Review Committee.* PC Code 147500. TXR No. 0053391. J. Kidwell. 5/18/05.
Residue Chemistry Summary:	*Pinoxaden in/on Wheat and Barley. PP# 4F6817. Summary of Analytical Chemistry and Residue Data.* M. Sahafeyan. 7/7/2005.
Dietary Analysis:	*Pinoxaden- Dietary Exposure Assessment for the Section 3 Registration Action.* M. Sahafeyan. D313800. 7/7/2005.
Occupational Assessment:	*PINOXADEN - Exposure/Risk Assessment for Pesticide Handlers Applying Pinoxaden to Barley and Wheat.* M. Dow. D315788. 4/13/2005.
Drinking Water Assessment:	*Drinking Water Assessment for pinoxaden use on wheat and barley.* I. Abdel-Saheb. D299583. 1/28/05.

Appendix 1. Toxicological Data Requirements

The requirements (40 CFR 158.340) for Food Use for pinoxaden are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	-
	Subchronic Oral (rat)	no	-
	Six-month Oral (dog)	no	-

Appendix 2. Non-Critical Toxicology Studies

MRID No. **Citation**

46203214. Sommer, E.. (2000) Acute Oral Toxicity Study in the Rat (Limit Test). Laboratory Study Identification: 20001076. Unpublished study prepared by Toxicology Novartis Crop Protection AG. August 10, 2000.

Executive Summary: In an acute oral toxicity study (MRID 46203214), 5/sex/dose Wistar rats (Age: 8 weeks, Weight: 185.9-199.4 g males, 162.6-176.8 g females; Source: RCC Ltd., Fullinsdorf, Switzerland) were given a single oral dose of pinoxaden technical(Propanoic acid: 97.2%; Batch #: EZ005006; beige solid) or a control dose of 0.5% w/v carboxymethylcellulose in 0.1% w/v polysorbate 80 by oral gavage. The study was performed at a limit dose of either 5,000 mg/kg or 0 mg/kg (control). Individual animal body-weights were recorded prior to dosing, and again on days 7 and 14. Clinical signs of toxicity were made several times post-dosing on the initial study day and daily thereafter for 14 days. All animals were necropsied on study day 14 or immediately after death.

Oral LD_{50} Males > 5,000 mg/kg
Females > 5,000 mg/kg
Combined > 5,000 mg/kg

Based on the LD_{50} in rats, pinoxaden technical is classified as EPA Toxicity Category IV.

All control animals survived, gained weight and appeared healthy during the study. No gross internal findings were observed at necropsy.

For those animals dosed at 5,000 mg/kg clinical signs of toxicity noted included slight soft feces and hunched posture, but animals recovered from these symptoms by day 1 of the study. One male was found dead on day 5 post-dosing. Gross necropsy of this animal revealed reddish small and large intestines and a reddish caecum. The surviving animals all gained weight during the study and had no gross internal findings at necropsy.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 401) in the rat. The report states that the animals were housed 5/sex/cage. According to OPPTS Guidelines 870.1100, the animals should be housed individually. These deviations did not affect the overall acceptability of the study.

46203219 Sommer. E. (2000) Acute Dermal Toxicity Study in the Rat. Laboratory Study Identification: 20001077. Unpublished study prepared by Toxicology Novartis Crop Protection AG. August 10, 2000..

Executive Summary: In an acute dermal toxicity study (MRID 46203219), 5/sex/dose Wistar rats (Age: 8-12 weeks; Weight: 216.4-246.5 g males, 207.1-220.8 g females; Source: RCC Ltd., Fullinsdorf, Switzerland), were dermally exposed to either a single application of pinoxaden technical(Propanoic acid: 97.2%; Batch #: EZ005006; beige solid) at 2,000 mg/kg or a control

dose of 0.5% w/v carboxymethylcellulose in 0.1% w/v polysorbate 80. The test material was evenly applied to the skin, distributed to be sure to cover at least 10% of the animal's BSA, by means of a semi-occlusive dressing around the trunk for 24 hours. Individual body-weights were recorded prior to testing and weekly thereafter Clinical checks for toxicity and dermal irritation were made several times post-dosing on the initial study day, and at least daily thereafter for 14 days. Checks for mortality were made twice daily. All animals were necropsied on study day 14.

Dermal LD_{50} Males > 2,000 mg/kg
Females > 2,000 mg/kg
Combined > 2,000 mg/kg

Based on the lack of mortality at 2,000 mg/kg, pinoxaden technicalis classified as EPA Toxicity Category III.

All animals survived and appeared healthy during the study. All control animals gained weight and had no gross necropsy findings at study termination. For those animals dosed at 2,000 mg/kg, slight weight loss was noted in 3 females during the first week, but all animals exceeded their initial body-weight by the end of the study period. At necropsy a slightly granulated kidney was noted in one male while a dilated left renal pelvis was noted in one female. No gross internal findings were observed at necropsy for the other animals.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

46203221 Decker, U. (2001) NOA 407855 tech.: 4-Hour Acute Inhalation Toxicity Study in Rats. Laboratory Study Identification: 780816. Unpublished study prepared by Toxicology Division RCC Ltd. July 5, 2001.

Executive Summary: In an acute inhalation toxicity study (MRID 46203221), 15/sex//dose Wistar rats (Age: 8-11 weeks; Weight: 237.8-260.3 g males; 190.4-220.9 g females; Source: RCC Ltd., Fullinsdorf, Switzerland) were exposed via nose-only, flow-past inhalation to pinoxaden technical(Propanoic acid: 97.2%; Batch #: EZ005006; solid) for 4 hours at analytically determined concentrations of either 2.249, 3.793 or 5.454 mg/L. The test was initiated at a concentration of 5.454 mg/L, but due to death in 50% of test animals, the dose was lowered to 2.249 mg/L. Based on the lack of deaths at this concentration the dose was raised to 3.793 mg/L in order to measure the LC_{50}. Individual body-weights were recorded prior to testing and on days 4, 8 and 15. The animals were observed for clinical signs of toxicity and mortality once per hour during the aerosol exposure period, after exposure and at least once a day thereafter for 15 days or until death. A gross necropsy examination was performed on all the animals on day 15 or when found dead.

LC_{50} Males = 4.63 mg/L (80% Confidence Limits: 3.35 – 20.68 mg/l air)
LC_{50} Females = 6.24 mg/L (No Confidence Limits calculated)
LC_{50} Combined = 5.22 mg/L (95% Confidence Limits: 4.07 -18.00 mg/l air)

Based on the LC_{50} of 4.63 mg/L for males, pinoxaden technicalis classified as EPA Toxicity Category IV.

For those animals dosed at 2.249 mg/L, all survived the study. Clinical signs of toxicity noted during and/or after exposure included laboured respiration, rales (breath sounds), salivation, ruffled fur, hunched posture and red secretion from the nose (in one animal). Symptoms of toxicity persisted until day 7 after exposure. The mean body-weight of the animals decreased during the first 4 days of the study but increased thereafter, exceeding their initial body-weight by the end of the study. Red discolouration of the lymph nodes was observed in two test animals at necropsy. No gross necropsy findings were found for the other test animals.

For those animals dosed at 3.793 mg/L, all survived the exposure period. 3/10 animals were found dead 2 days after the exposure period. Clinical signs of toxicity noted during and/or after exposure included tachypnea, laboured respiration, rales (breath sounds), salivation, ruffled fur, hunched posture, restlessness and decreased activity. In one female a swollen abdomen was also observed. Symptoms of toxicity persisted until day 7 after exposure. The mean body-weight of the surviving animals decreased during the first 4 days of the study but increased thereafter, exceeding their initial body-weight by the end of the study. Red discolouration of the lungs was observed at necropsy in 2/3 of the test animals that died during the study. No gross necropsy findings were found for the other test animals.

For those animals dosed at 5.454 mg/L, all survived the exposure period. 4/10 animals were found dead the day after the exposure period. A fifth animal was found dead 3 days after the exposure period. Clinical signs of toxicity noted during and/or after exposure included bradypnea, laboured respiration, rales (breath sounds), salivation, ruffled fur, hunched posture, restlessness and decreased activity. Symptoms of toxicity persisted up to day 7 after exposure. The mean body-weight of the surviving animals decreased during the first 4 days of the study but increased thereafter. Males exceeded their initial body-weight by the end of the study while females exceeded their initial body-weight. Red discolouration of the lungs was observed at necropsy in 4/5 of the test animals that died during the study. The other test animal that died had several dark red foci in the thymus at necropsy. One surviving animal had incompletely collapsed lungs at necropsy. No gross necropsy findings were found for the other test animals.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

46203223 Arcelin, G. (2000) NOA 407855 tech.: Primary Eye Irritation Study in Rabbits. Laboratory Study Identification: 780794. Unpublished study prepared by Toxicology Division RCC Ltd. December 7, 2000.

Executive Summary: In a primary eye irritation study (MRID 46203223), 1.0 g of pinoxaden technical(Propanoic acid: 97.2%; Batch #: EZ005006; solid) was instilled into the conjunctival sac of the left eye of 3 young adult New Zealand albino rabbits (Source: Elevage Scientifique des Dombes, Chatillon sur Chalaronne, France). The test substance was applied as received from the sponsor. The untreated right eye served as a control. Animals were then observed at 1, 24, 48, 72 hours and 7, 10, 14, 17 and 21 days post-instillation. Additional observations at 24 and 28 days were made for 2 of the animals. Irritation was scored according to Draize. Observations for clinical signs of toxicity and mortality occurred daily.

In this study, the formulation is irritating to the eye. Pinoxaden technicalis classified as EPA Toxicity Category I.

One hour after instillation all 3 eyes exhibited corneal opacity (score 1). This irritation persisted in one animal to 72 hours and in a second to 7 days. In the third animal the opacity increased in severity (score 2) at day 7 and increased further (score 3) at 17 days. This irritation persisted through 24 days. One hour after instillation all 3 eyes also exhibited conjunctivitis scores of 1 for redness and 2-3 for chemosis. "Assessment of the sclera could not be performed on a number of occasions due to swelling of the conjunctivae and/or the production of mucus." This irritation persisted up through 21 days in one animal. Discharge was noted 1 hour after instillation and persisted up to 17 days after treatment in one female. "Yellow and beige remnants of the test item were evident in the eye or conjuctival sac in all animals at the 1-hour reading. This persisted in one animal up to 48 hours after treatment." All animals were free from ocular irritation by 28 days. No corrosion, iritis or signs of toxicity were noted during the study.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

46203225 Arcelin, G. (2000) NOA 407855 tech.: Primary Skin Irritation Study in Rabbits. Laboratory Study Identification: 780783. Unpublished study prepared by Toxicology Division RCC Ltd.. October 5, 2000.

Executive Summary: In a primary dermal irritation study (MRID 46203225), 3 young adult New Zealand albino rabbits (1 male, 2 females; Source: Elevage Scientifique des Dombes, Chatillon sur Chalaronne, France) were dermally exposed to 0.5 g of pinoxaden technical(Propanoic acid: 97.2%; Batch #: EZ005006; solid). The test substance was moistened with 0.1 mL if bi-distilled water, placed on a 6 cm^2 area of a gauze pad, applied to the left flank on each animal and secured with a semi-occlusive wrap for 4 hours. Animals were then observed for 72 hours. Dermal irritation was scored according to the Draize system at 1, 24, 48 and 72 hours post-patch removal. Observations for clinical signs of toxicity and mortality occurred daily.

In this study, the formulation is non-irritating to the skin. Pinoxaden technicalis classified as EPA Toxicity Category IV.

No erythema or edema were noted at any point during the study. PII is 0.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

46203227 Arcelin, G. (2000) NOA 407855 tech.: Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test. Laboratory Study Identification: 780805. Unpublished study prepared by Toxicology Division RCC Ltd. November 30, 2000. MRID.

Executive Summary: In a dermal sensitization study (MRID 46203227) with pinoxaden technical(Propanoic acid: 97.2%; Batch #: EZ005006; solid), 15/sex (5/sex for control and

10/sex for test) Himalayan spotted guinea pigs (Weight: 309-376 g males, 298-403 g females Source: RCC Ltd., Fullinsdorf, Switzerland) were tested using the Magnusson-Kligman Design method.

During the preliminary testing phase, appropriate concentrations of the test substance to be used were determined for the intradermal induction (test substance at 5% in vehicle (0.5% CMC + 0.1% Tween 80 in bi-distilled water)), topical induction (test substance at 50 % in vehicle), and topical challenge (test substance at 50 % in vehicle).

The first induction phase involved 3, 0.1 mL intradermal paired injections into 20 guinea pigs of the test substance (test substance at 5% in vehicle), test substance and Freund's Adjuvant, and Adjuvant alone. Paired injections were also administered to 10 control guinea pigs of the vehicle, vehicle with Freund's Adjuvant, and Adjuvant alone.

One week later, a second induction phase was conducted consisting of a 0.3 mL topical application of the test substance at 50 % in vehicle applied to a patch of filter paper and placed on the dose site of the test animals, which was then covered for 48 hours. Twenty-four and 48 hours after patch removal the animals were scored for erythema. The control group was treated in the same manor with vehicle only. Twenty-three hours prior to this phase the animals were treated with 0.5 mL of 10% SLS to provoke a mild inflammatory reaction.

Two weeks after the topical application of the induction phase the challenge phase was conducted by applying 0.2 g of a topical application of the test substance at 50 % in vehicle on the left flank, and 0.2 mL of vehicle only on the right flank, to both the test and control guinea pigs for 24 hours. Twenty-four and 48 hours after patch removal the animals were scored for erythema.

Observations for clinical signs of toxicity and mortality occurred daily.

The procedures were validated using 2-Mercaptobenzothiazole as the positive control substance.

Based on this study, pinoxaden technicalis not a dermal sensitizer and does not have to be labelled as such.

During the induction phase, observations at all dose sites for test animals treated with the test substance during the topical application phases revealed discrete/patchy erythema (score 1) at 24 hours and in 18/19 animals at 48 hours. This reaction was also noted in the control animals at 24 and 48 hours after treatment with vehicle only. One test male died on test day 10 after removal of the dressing in the topical induction phase. Gross necropsy of this animal revealed no internal findings. At challenge no skin reactions were noted for either the test or the control animals.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig.

46203235 Twomey, K. (2003) NOA 407855: 90 Day Dietary Toxicity Study in the Rat with a 28 Day Interim Kill: Final Report. Project Number: PR1254, CTL/PR1254/REG/REPT. Unpublished study prepared by Central Toxicology

Lab (Syngenta). 1569 p.

Executive Summary - In this subchronic oral toxicity study (MRIDs 46203235 and 46203237), 12 Alpk:APfSD rats/sex/dose were exposed to pinoxaden (97.2% a.i.; Batch #: EZ005006) in the diet at concentrations of 0, 150, 1000, 5000, or 10,000 ppm nominally (equivalent to 0/0, 15/16, 98/110, 466/527, and 900/965 mg/kg/day in males/females) for up to 90 days. An additional 5 rats/sex/dose were treated similarly and sacrificed at day 28 (interim study).

There were no treatment-related effects on mortality, clinical signs, functional observational battery, motor activity, food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, organ weights, or gross pathology.

At 10,000 ppm (n=12) in the main study, body-weights were decreased ($p \leq 0.05$) throughout the study in both sexes (decreased 4-19%), and overall (weeks 1-14) body-weight gains were decreased (decreased 9-16%). Food consumption was decreased ($p \leq 0.05$) in males during the first week (excluding day 6) by 16-72% and during weeks 2, 3, 8, and 11-13 by 6-10%. Increased ($p \leq 0.05$) water consumption was observed in the males during the first 7 weeks (excluding week 4) by 13-46%. Urine volume was increased ($p \leq 0.01$) by 54% in the females. Renal lesions were observed (minimal to slight # affected/12 treated vs 0/12 controls) as follows: (I) cyst(s) in both sexes (7-10); (ii) cortical tubular basophilia/dilatation/atrophy in both sexes (6-8); (iii) ectasia pelvis in males (2); and (iv) transitional cell hyperplasia in males (2).

In the interim study, cortical tubular basophilia/dilatation/atrophy was observed in 2/4 males and 1/5 females at 10,000 ppm vs 0/5 controls. Cholesterol was decreased ($p \leq 0.05$) in the 10,000 ppm group by 19-20%. Generally similar effects were observed on body-weight, body-weight gain, and food consumption in the interim study compared to the main study.

The LOAEL was 10,000 ppm (equivalent to 900/965 mg/kg/day in males/females), based on decreased body-weight and body-weight gain and increased incidence of renal lesions in both sexes; decreased food consumption and increased water consumption in males; and increased urine volume in females. The NOAEL is 5000 ppm (equivalent to 466/527 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

46203239 Twomey, K. (2003) 90-Day Oral Toxicity Study in Rats (Gavage) (Includes Report Amendments 1 and 2): NOA 407855 Technical: Final Report. Project Number: 991092, 1313/99, 761253. Unpublished study prepared by Syngenta Crop Protection, Novartis Crop Protection and Preclinical Safety Consultants Ltd. 711 p.

Executive Summary - In this subchronic oral toxicity study (MRIDs 46203239, 46203229, and 46203234), pinoxaden (95.7% a.i.; Batch #: 1192-PH-10) in 0.5% carboxymethylcellulose, 0.1 % Tween 80 in distilled water was administered by daily gavage at a dose volume of 10 mL/kg bw to 10 HanIbm:WIST rats/sex/group at doses of 0, 3, 10, 30, 100, or 300 mg/kg/day) for 3 months. Additionally, 10 rats/sex were treated similarly at 0, 100, or 300 mg/kg/day for 3 months and

allowed to recover for 4 weeks without treatment.

There were no treatment-related effects observed on mortality, clinical signs, body-weight, body-weight gain, food consumption and efficiency, ophthalmology, hematology, organ weights, or gross and histologic pathology.

In the ≥100 mg/kg/day females, increases ($p \leq 0.05$) were observed in serum potassium (incr 7-12%) and inorganic phosphate (incr 20-25%) levels.

In the 300 mg/kg/day males, glucose was decreased ($p \leq 0.01$) by 16%, and increased ($p \leq 0.05$) water consumption was observed during weeks 3-5 and 8-9 (incr 18-27%). An increased frequency of renal corticomedullary mineralization was observed in males (5/10 treated vs 2/10 controls); however, severity was decreased (minimal at 300 mg/kg/day vs slight in the controls for all affected rats). Additionally, in the 300 mg/kg/day females, increased ($p \leq 0.05$) water consumption was observed (incr 14-29%) throughout most of the study, and urinary volume was increased ($p \leq 0.01$) by 53%. Creatinine was increased ($p \leq 0.01$) by 18% in the 300 mg/kg/day females. Nephrotoxicity was indicated in females by increased water consumption, urinary volume and increased creatinine.

The LOAEL was not observed in males; however, the LOAEL was 300 mg/kg bw/day in females based on increases in water consumption, urinary volume and creatinine (indicators of nephrotoxicity) in females. The NOAEL is 300 mg/kg bw/day in males and 100 mg/kg bw/day in females.

This study is classified as **Acceptable/guideline** and does satisfy the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat. A LOAEL was not observed in males; however, the Sponsor submitted an acceptable/guideline 90-day dietary study (MRID 46203235).

46203241 Bachmann, M. (2002) 90-Day Rangefinding Toxicity Study in Mice (Gavage): NOA 407855: Final Report. Project Number: 20001128, 785305. Unpublished study prepared by RCC Ltd. and RCC Umweltchemie Ag. 418 p.

Executive Summary - In this subchronic oral toxicity study (MRID 46203241), pinoxaden (97.2% a.i.; Batch #: EZ005006) in 0.5% carboxymethylcellulose, 0.1 % Tween 80 in distilled water was administered for 3 months by daily gavage at a dose volume of 10 mL/kg bw to Crl:CD®-1(ICR)BR mice (10/sex/group) at doses of 0, 10, 100, 400, 700, or 1000 mg/kg bw/day. A functional observational battery was also conducted where the animals were evaluated in the home cage, open field, and during handling.

No treatment-related effect was observed on mortality, food consumption, water consumption, hematology, organ weight, or gross pathology.

At 1000 mg/kg bw/day, piloerection (neck fur raised) was observed at the cageside in both sexes (50-80% treated vs 0-10% controls) and during the FOB (n=10) at an increased incidence in 2-5 males on weeks 1 and 3-6, and 4 females on week 3 and 1 female on weeks 4 and 9. Although there were no significant ($p \leq 0.05$) decreases in body-weights or body-weight gains, overall (days

1-92) body-weight gain was decreased (not statistically significant) by 60-67% in the 1000 mg/kg bw/day group. Renal tubular basophilia was increased in incidence in the males (4/10 treated vs 1/10 controls) and also in severity (minimal to marked in treated vs slight in controls).

The LOAEL is 1000 mg/kg bw/day, based on increased incidence of piloerection and decreased body-weight gain in both sexes, and increased incidence of renal tubular basophilia in males. The NOAEL is 700 mg/kg bw/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the mouse.

46203242 Lees, D. (2003) NOA 407855 Tech.: 90 day oral toxicity in dogs. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study Identification: CTL Study Number PD1225, July 24, 2003. Unpublished.

Executive Summary - In a subchronic oral study (MRIDs 46203242 and 46203230), pinoxaden technical (97.2% a.i., Batch #: EZ005006) was administered neat in gelatin capsules to 4 beagle dogs/sex/dose at doses of 0, 25, 100, 250, or 500 mg/kg bw/day for up to 14 weeks.

There were no treatment-related effects on survival, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights, or gross pathology.

At 500 mg/kg bw/day, all 4 females were killed for humane reasons in week 5, and 1 male displaying clinical signs of toxicity, body-weight loss, and decreased food consumption was killed prior to scheduled sacrifice during week 13. All other animals survived to scheduled sacrifice.

At ≥250 mg/kg bw/day, increased incidences of fluid feces, vomit, pale and thin appearance, decreased activity, dehydration, cold to touch, and regurgitation were observed in both sexes. Mucus in feces was observed in the males. At 250 mg/kg bw/day, veterinary examinations performed at week 13 revealed 1 male to have a slow pulse rate; another male was described as appearing depressed and thin. One female was examined several times and had findings that included thin appearance, cold to touch, dehydrated, mucus membranes pale, extremities cold to touch, and a quiet and slow heart beat.

Body-weights (decreased 1-12%; not significant) and food consumption (decreased 1-52%; NS) were generally decreased in the 250 mg/kg bw/day and above groups throughout treatment. Overall (weeks 1-14) body-weight gains (calculated by reviewers) were decreased by 32-75% in the 250 mg/kg bw/day group. In the 500 mg/kg bw/day females, body-weights were decreased ($p \leq 0.01$) by 12% on week 5, and food consumption was decreased ($p \leq 0.05$) by 24-52% during weeks 4-5.

The LOAEL for this study is 250 mg/kg bw/day based on clinical signs of toxicity (fluid feces, vomit, pale and thin appearance, decreased activity, dehydration, cold to touch, and regurgitation in both sexes, and mucus in feces in the males) and decreased body-weights, body-weight gains, and food consumption in both sexes. The NOAEL is 100 mg/kg bw/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3150; OECD 409) for a 90-day oral toxicity study in the dog.

46203243 Sommer, E.W. (2001) 28-day repeated dose dermal toxicity study in rats. Syngenta Crop Protection, AG, Stein, Switzerland. Laboratory Study Id.: RCC No. 20001186, December 20, 2001. Unpublished.

Executive Summary: In a 28-day dermal toxicity study (MRID 46203243), Pinoxaden technical (97.2% a.i.; Batch # EZ005006) in aqueous 1% carboxymethyl-cellulose/0.1% Tween 80 was applied to the shaved intact skin of 10 HanBrl:WIST rats/sex/dose at dose levels of 0, 10, 100, or 1000 mg/kg bw/day. The rats were treated daily during a 28-day period (except the weekends for the first 3 weeks) for 6 hours/day.

No treatment-related effects were observed in mortality, clinical signs, neurological evaluations, dermal irritation, body-weight, body-weight gain, food consumption and efficiency, water consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, or macroscopic or histological pathology at any dose in either sex.

The LOAEL was not observed. The NOAEL is 1000 mg/kg bw/day (the limit dose).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3200; OECD 410) for a 28-day dermal toxicity study in rats. The LOAEL was not observed; however, the compound was tested to the limit dose.

46203309 Lees, D. (2003) NOA 407855 Tech.: 1 year oral toxicity study in dogs. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study ID.: CTL Number PD1226, October 13, 2003. Unpublished.

Executive Summary - In a chronic oral toxicity study (MRID 46203309), Pinoxaden (Batch #: EZ005006; 97.2% a.i.) was administered neat in gelatin capsules to 4 beagle dogs/sex/dose at nominal doses of 0, 5, 25, or 125 mg/kg bw/day for up to 53 weeks.

There were no effects of treatment on mortality, clinical signs, body-weight or body-weight gains, food consumption, ophthalmoscopic examination, hematology, urinalysis, organ weights, gross pathology, or histopathology.

At 25 mg/kg bw/day, increased incidence of fluid feces was noted in the males and salivation at dosing was observed in the females. At 125 mg/kg bw/day, increased incidence of fluid feces, salivation at dosing, vomit, and mucus in the feces were observed in both sexes. However, in the absence of corroborating findings, these observations were not considered to be of toxicological significance.

Alkaline phosphatase was increased in the 125 mg/kg bw/day males at week 52 (↑75%; $p \leq 0.05$), in the 25 mg/kg bw/day females at week 13 (↑26%; $p \leq 0.05$), and in the 125 mg/kg bw/day females at weeks 13, 26, and 52 (↑55-112%; $p \leq 0.01$). However, this finding was considered equivocal, as no corroborating alterations in organ weight or pathology were observed.

The LOAEL was not observed. The NOAEL is 125 mg/kg bw/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.4100b, OECD 452) for a chronic oral toxicity study in dogs. A LOAEL was not observed, and animals were not dosed to the limit dose (1000 mg/kg bw/day). However, a LOAEL of 250 mg/kg bw/day was observed in the subchronic study, and the stated dose rationale, while overly cautious, was reasonable. Therefore, this study is considered acceptable.

46203311 Lees, D. (2004) NOA 407855: Study to investigate the effects of direct administration of compound to mouse lung parenchyma (Revision - 001). Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study Identification: CTL Number XM7083, January 19, 2004. Unpublished.

Executive Summary: In the first of 2 non-guideline studies (MRID 46203311), the lung parenchyma of male mice (strain and source not provided) was: I) exposed to Pinoxaden (97.2% a.i.; Lot/Batch #: EZ005006) in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous Tween 80 vehicle; ii) exposed to the vehicle alone; or iii) left untreated. Groups of 2 mice were killed and their lungs removed. The lungs were then directly dosed via a syringe with 250 µL of either a 75 mg/mL formulation (approximately equivalent to a whole animal dose of 750 mg/kg/day) or vehicle. Lungs from 2 untreated mice served as an additional control group. One pair of lungs from each group was then fixed after 1 minute of exposure; the other pair was fixed after 10 minutes of exposure. Lung sections from all animals were examined microscopically. The objective of this study was to investigate the histopathological effects of direct administration of Pinoxaden in vehicle on the lung parenchyma of male mice.

It was stated that it was physically easier to instill vehicle into the lungs than the 75 mg/mL dose formulation. The test substance was observed to block the lung passages, making introduction of additional material difficult. Untreated lungs and lungs treated with vehicle only were similar in appearance. Lungs that were dosed with 75 mg/mL Pinoxaden were observed to be pale and were difficult to inflate with formol saline. Reduced eosinophilic staining of the alveolar walls was observed in lungs dosed with 75 mg/mL Pinoxaden and vehicle only following 1 and 10 minute exposures. Lysis of intravascular red blood cells was noted in lungs dosed with 75 mg/mL Pinoxaden and vehicle after the 10 minute exposure.

In the second of 2 non-guideline studies (MRID 46224806), male CD-1® [Crl:CD-1®(ICR)BR] mice (5/group) were dosed by oral gavage with 0.5% (w/v) carboxymethylcellulose in 0.1% aqueous Tween 80 vehicle containing 1.0% (w/v) Evans Blue dye. The dosing catheters were either normal (having an opening near the bottom to deliver the dose to the stomach), modified so that the opening was higher on the catheter to deliver the dose to 1 of 2 locations in the esophagus (low and high esophagus), or modified so that the opening was higher on the catheter and the catheter was shorter in overall length (modified high esophagus). Mice were killed approximately 0.5 hours after dosing, the thoracic cavity was opened, and the location of the dye was recorded. The lungs and trachea were removed, observed for location and intensity of dye appearance, photographed, and fixed. Sections were prepared from all lungs and examined microscopically. Based on these results, on the following day (day 2 animals) additional groups of 5 mice were dosed with the carboxymethylcellulose-Tween 80 vehicle without dye using either a normal or high esophagus catheter. High esophagus mice were killed at 1, 24, or 72

hours after dosing; normal catheter and untreated mice were killed at 72 hours after dosing. The lungs and trachea were removed, observed, fixed, sectioned, and examined microscopically. The objective of this study was to develop an experimental model to investigate the effects of carboxymethylcellulose/Tween 80 vehicle on the lungs of male mice.

On day 1, vehicle was observed in the mouth of all group 3 (high esophagus) mice immediately after dosing. One of these animals then died and was not replaced. Dye was observed in the airways of 1/5 group 2 (low esophagus), 4/5 group 3 (high esophagus), 1/5 group 4 (modified high esophagus, 5 mL/kg dose volume), and 2/5 group 5 (modified high esophagus, 10 mL/kg dose volume) mice. Microscopically, minimal to slight hemorrhage was observed in 1/5 group 1 (normal esophagus), 1/5 group 2, 2/5 group 3 and 1/5 group 5 mice, but the significance of this finding was unclear. Also in these mice, minimal hyaline change was noted in 1/5 group 3 and 1/5 group 5 mice.

On day 2, vehicle was observed in the mouth of all group 3, 4, and 5 (high esophagus) mice immediately after dosing. One group 5 (high esophagus, 72 hours post-dosing) mouse died immediately after dosing and was replaced to maintain 5 mice/group. A second group 5 mouse was found in moribund condition approximately 69.5 hours after dosing and died shortly thereafter. This animal was examined by the same procedures as those killed on schedule. One group 5 (high esophagus, 72 hours post-dosing) was noted to have areas of dark blue coloration in all lung lobes. It was thought this finding was linked to the clinical condition of this animal (found moribund and died prior to 72 hours). Microscopically, 1/5 group 3 mice had a small focus of acute pneumonitis, consistent with aspiration of the vehicle. In group 4, 2/5 mice were observed to have slight esophagitis, consistent with dosing trauma. In group 5, 2/5 mice died prior to termination. One of these animals demonstrated slight hemorrhage with minimal hyaline change. This animal was replaced. The second mouse was found to have severe pleuritis consistent with esophageal rupture and application of the vehicle into the mediastinum.

Collectively, the data indicate that carboxymethylcellulose Tween-80 vehicle used during oral gavage dosing may contribute to the pathological changes observed in the 80-week carcinogenicity study (MRID 46224808).

The submitted studies are classified as **unacceptable/non-guideline due to major technical and scientific deficiencies.**

46203314 Sokolowski, A. (2001) Salmonella Typhimurium and Escherichia coli Reverse Mutation Assay with NOA 407855 Tech.: Final Report. Project Number: 672909, 784383, 20001072. Unpublished study prepared by RCC Umweltchemie Gmbh & Co. Kg and RCC Umweltchemie Ag. 84 p.

Executive Summary - In two independent reverse gene mutation assays in bacteria (MRID 46203314), *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 and *Escherichia coli* strain WP2*uvr*A were exposed to Pinoxaden technical (97.2% a.i., Batch # EZ005006) in dimethylsulfoxide (DMSO) at concentrations of 33, 100, 333, 1000, 2500, or 5000 µg/plate in the presence and absence of mammalian metabolic activation (+/-S9). The standard plate incorporation method was performed in Trial 1 (+/-S9), while a pre-incubation step was

added in Trial 2 (+/-S9). Standard strain-specific mutagens served as positive controls.

Pinoxaden technical was tested up to the limit dose (5000 µg/plate). In Trial 1, cytotoxicity (as indicated by reduction in number of revertants) was observed at ≥1000 µg/plate (TA100 and TA102, -S9) and at ≥2500 µg/plate (TA1535, -S9; and TA98, TA100, and TA102, +S9). In Trial 2, cytotoxicity was observed at ≥1000 µg/plate (TA100 and TA102, -S9; and TA1537, +S9), at ≥2500 µg/plate (TA1537, -S9; and TA100 and TA102, +S9), and at 5000 µg/plate (TA98, +/-S9). Normal background lawn growth was observed at all concentrations in all strains in both trials. No marked increases in the number of revertants were observed at any concentration in any strain in either trial. The positive controls induced marked increases in revertant colonies compared to controls in both trials. **There was no evidence of induced mutant colonies over background.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

46203318 Wollny, H. (2003) Cell Mutation Assay at the Thymidine Kinase Locus (TK+/-) in Mouse Lymphoma L5178Y Cells with Pinoxaden Tech.: Final Report. Project Number: 672905, 20001074, 781470. Unpublished study prepared by RCC Umweltchemie Gmbh & Co. Kg, RCC Umweltchemie Ag and Novartis Crop Protection. 125 p.

Executive Summary - In three independent trials of a mammalian cell gene mutation assay at the $TK^{+/-}$ locus (MRID 46203318), L5178Y mouse lymphoma cells cultured *in vitro* were exposed to Pinoxaden technical (97.2% a.i., Batch # EZ005006) in acetone for either 4 hours at concentrations of 6.3, 12.5, 25, 50, 100, or 200 µg/mL (Trial 1 -S9) or 3.1, 6.3, 12.5, 25, 50, or 100 µg/mL (Trial 1 +S9); or for 24 hours at concentrations of 25, 50, 100, 200, 300, or 400 µg/mL (Trial 2 -S9). Due to insufficient cell growth in the negative and solvent control second cultures in the second cultures of Trial 1 (+S9), a repeat trial was performed at 6.3, 12.5, 25, 50, 100, or 150 µg/mL (+S9) and was reported as Trial 1A. In Trial 2, the negative control of the second culture exceeded the historical range and the positive control induced excessive cytotoxicity; therefore, this part of the trial was repeated at the same doses and reported as Trial 2A. A third trial was performed at 3.1, 6.3, 12.5, 25, 50, or 100 µg/mL (+S9) to confirm the results observed in Trials 1 and 1A in the presence of S9. Methylmethane sulfonate (MMS) and 3-Methylcholanthrene (3-MC) served as positive controls in the absence and presence of S9, respectively.

Pinoxaden was tested up to cytotoxic concentrations (≥50 µg/mL, +S9) and (≥100 µg/mL,-S9). No reproducible substantial (≥2x solvent controls) and/or concentration-dependent increases in mutant colonies per 10^6 cells were observed at any dose level in the presence or absence of S9. The positive controls induced the expected response. **There was no evidence of induced mutant colonies over background.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.5300, OECD 476) for *in vitro* mutagenicity (mammalian forward gene mutation) data.

46203321 Czich, A. (2001) *In vitro* Chromosome Aberration Test in Chinese Hamster V79 Cells with Pinoxaden Tech.: Final Report. Project Number: 672907, 20001073, 784258. Unpublished study prepared by RCC Umweltchemie Gmbh & Co. Kg, RCC Umweltchemie Ag and Novartis Crop Protection AG. 98 p.

Executive Summary - In three independent trials of a mammalian cell cytogenetics assay (chromosome aberration; MRID 46203321), Chinese hamster V79 cultures were exposed to pinoxaden (97.2% a.i., Batch # EZ005006) in acetone at concentrations of 6.3, 12.5, 25, 50, 75, or 100 µg/mL (Trial 1, 4 hr exposure and 14 hour recovery period prior to cell harvest); 10, 20, 40, 60, 80, or 100 µg/mL (Trial 2, 18 hr exposure); and 40, 60, 80, or 100 µg/mL (Trial 2, 28 hr exposure) in the absence of S9. In the presence of S9, cultures were exposed for 4 hours at concentrations of 10, 20, 40, 60, 80, or 100 µg/mL (Trial 1, 14 hour recovery period prior to cell harvest) and 30, 40, 50, 60, 70, or 80 µg/mL (Trial 2, 24 hour recovery period prior to cell harvest). Additionally, to clarify the results observed in Trials 1 and 2, a third trial was performed at concentrations of 12.5, 25, 50, 75, 100, or 125 µg/mL (4 hr exposure with 18 hour recovery and 18 hr exposure) in the absence of S9 and 20, 40, 60, 80, 100, or 120 µg/mL (4 hr exposure with a 24 hour recovery period prior to cell harvest) in the presence of S9.

Pinoxaden was tested up to cytotoxic concentrations (≥ µg/mL +S9; and ≥80 µg/mL -S9). In the presence of S9, increases ($p \leq 001$) in the percent aberrant cells (excluding gaps) were observed after 4 hours treatment and 24 hours recovery in Trial 2 at ≥60 µg/mL (7.0-11.0% treated vs 1.0% solvent control) and in Trial 3 at 60 µg/mL (11.5% treated vs 0.5% solvent control). In the absence of S9, increases ($p \leq 0.05$) in the percent aberrant cells (excluding gaps) were observed after 4 hours treatment and 14 hours recovery in Trial 1 at >=25 µg/mL (2.5-7.5% treated vs 0% solvent control) and in Trial 3 at ≥75 µg/mL (2.5-3.5% treated vs 0% solvent control); and after 18 hours of continuous exposure in Trial 2 at ≥80 µg/mL (2.5-5.5% treated vs 0% control) and in Trial 3 at ≥100 µg/mL (4.0-8.0% treated vs 0.5% control). Although there was not a clear dose-response and several of the increases in percent aberrant cells were within the historical control range (0.0-4.0%), there was sufficient reproducible evidence of a positive mutagenic effect in the presence and absence of S9. No biologically relevant increases in the rate of polyploid metaphases were observed at any concentration in any trial (+/-S9). The positive controls induced the appropriate response. **There was evidence that Pinoxaden induced a clastogenic effect in the presence and absence of S9-activation.**

This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

46203322 Schulz, M. (2002) *In vitro* Chromosome Aberration Test in Chinese Hamster V79 Cells with Pinoxaden: Final Report. Project Number: 702901, 20011070, 825017. Unpublished study prepared by RCC Umweltchemie Gmbh & Co. Kg and RCC Umweltchemie Ag. 99 p.

Executive Summary - In three independent trials of a mammalian cell cytogenetics assay (chromosome aberration; MRID 46203322), Chinese hamster V79 cultures were exposed to pinoxaden (99.5% a.i., Batch # AMS 1055/2) in acetone for 4 hours (with a 14 hr recovery period prior to cell harvest) at concentrations of 15, 30, 45, 60, 75, and 90 µg/mL (Trials 1A and 1B, -

S9); 3.8, 7.5, 15, 30, 45, and 60 µg/mL (Trial 1A, +S9); and 7.5, 15, 30, 45, 60, and 90 µg/mL (Trial 1B, +S9). Additionally, to clarify the results observed in Trials 1A and 1B, a third trial was performed at concentrations of 10, 20, 40, 60, 80, or 100 µg/mL (18 hr continuous exposure, -S9); 40, 60, 80, or 100 µg/mL (28 hr continuous exposure, -S9); and 7.5, 15, 30, 45, 60, and 90 µg/mL (4 hr exposure with a 24 hour recovery period prior to cell harvest, +S9).

Pinoxaden was tested up to cytotoxic concentrations (≥45 µg/mL +S9; and ≥75 µg/mL -S9). In the presence of S9, increases ($p \leq 0.001$) in the percent aberrant cells (excluding gaps) that exceeded the historical control range were observed after 4 hours treatment with 14 hours recovery in Trial 1A at 60 µg/mL (9.0% treated vs 1.5% solvent control) and after 4 hours treatment with 24 hours recovery in Trial 2 at 45 µg/mL (10.5% treated vs 0% solvent control). In the absence of S9, increases ($p \leq 0.01$) in the percent aberrant cells (excluding gaps) that exceeded the historical control range were observed after 4 hours treatment with 14 hours recovery in Trial 1A at 90 µg/mL (12.0% treated vs 1.0% solvent control) and in Trial 1B at 90 µg/mL (11.5% treated vs 0.5% solvent control); and after 18 hours of continuous exposure in Trial 2 at 100 µg/mL (8.0% treated vs 2.0% control). No biologically relevant increases in the rate of polyploid metaphases were observed at any concentration in any trial (+/-S9). The positive controls induced the appropriate response. **There was evidence that Pinoxaden induced a clastogenic effect in the presence and absence of S9-activation.**

This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

46203324 Fox, V. (2003) SYN 502836 (Metabolite of Pinoxaden): *In vitro* Cytogenetic Assay in Human Lymphocytes: Final Report. Project Number: SV1141. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 33 p.

Executive Summary - In two independent trials of a mammalian cell cytogenetics assay (chromosome aberration; MRID 46203324), lymphocyte cultures were prepared from human peripheral blood and exposed to SYN 502836 (a metabolite of Pinoxaden tech.; pinoxaden; 99% a.i., Batch # KI 6513/3M) in dimethylsulfoxide (DMSO) at concentrations of 50, 100, 200, 500, 1000, 1500, 2000, and 2750 µg/mL for either 3 hours with a 17 hour recovery period (Trial 1, +/-S9 and Trial 2, +S9) or 20 hours with no recovery period (Trial 2, -S9).

SYN 502836 was tested up to a maximum concentration of 2000 µg/mL (+/-S9), which was limited by reductions in the pH of the treatment medium. Cytotoxicity (as evidenced by reduced mitotic index) was noted at ≥1000 µg/mL in Trial 1 (+S9) and at 2000 µg/mL in Trial 2 (+/-S9). No significant increases in aberration frequencies (excluding gaps) were observed in the presence or absence of S9 in either trial. The positive controls induced the appropriate response in all assays. **There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.**

This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

46203325 Clay, P. (2002) NOA 407855: *in vivo* Rat Liver Unscheduled DNA Synthesis Assay: Final Report. Project Number: SR1130. Unpublished study prepared by

Central Toxicology Lab. (Syngenta). 31 p.

Executive Summary - In an *in vitro/in vivo* unscheduled DNA synthesis assay (MRID 46203325), rat hepatocyte cultures were prepared from 3 male (Alpk:AP$_f$SD) rats/sacrifice time that were treated orally (gavage, 10 mL/kg) once with pinoxaden (97.2% a.i., Batch # EZ005006) in 0.5% aqueous carboxymethylcellulose at a dose of 2000 mg/kg (limit dose). Hepatocytes were harvested after 2 or 16 hours of exposure. Additionally, 2 rats/sacrifice time were treated with the vehicle or positive control (1,2-dimethylhydrazine dihydrochloride).

pinoxaden was tested up to the limit dose (2000 mg/kg). There were no clinical signs of toxicity in the treated animals or evidence of excessive cytotoxicity in any of the cultures. There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG $\geq$5) at 2 or 16 hours post-dosing compared to controls. The positive control induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.**

The study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5550; OECD 486) for other genotoxic mutagenicity data. Although, the dosing formulation was not analyzed for the amount of test substance, this is not considered to be a major deficiency that would have altered the results of the study, since the limit dose was tested and the testing laboratory adheres to GLP regulations, and has a QA unit.

46203327 Honarvar, N. (2001) Micronucleus Assay in Bone Marrow Cells of the Mouse with Pinoxaden tech.: Final Report. Project Number: 672901, 20001070, 780671. Unpublished study prepared by Cytotest Cell Research Gmbh and Co. and RCC Umweltchemie Ag. 67 p.

Executive Summary - In a bone marrow micronucleus assay (MRID 46203327), 6 fasted NMRI mice/sex/dose were treated once via gavage (10 mL/kg) with Pinoxaden (Pinoxaden; 97.2% a.i., Batch # EZ005006) dissolved in 40% ethanol in PEG 400 at doses of 0, 500, 1000, or 2000 mg/kg bw. Bone marrow cells were harvested from all animals and samples from 5 mice/sex/dose at 24 (all doses) or 48 hours (2000 mg/kg only) post-dosing were evaluated. Cyclophosphamide (40 mg/kg) served as the positive control.

Pinoxaden was tested up to the limit dose (2000 mg/kg); however, no evidence of bone marrow toxicity (decreased PCE:NCE) was observed at the 24 or 48 hour sampling times at up to 2000 mg/kg. No significant increase in micronucleated polychromatic erythrocytes (MPCEs) was observed in any dose at either 24 or 48 hours post-dosing. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirement (OPPTS 870.5395; OECD 474) for *in vivo* cytogenetic mutagenicity data.

46203329 Schultz, M. (2001) Unscheduled DNA synthesis in primary hepatocytes of male rats *in vitro* with NOA 407855 technical RCC - Cytotest Cell Research GmbH,

Roßdorf, Germany. Laboratory Study ID: RCC-CCR Study Number 672903, January 16, 2001. Unpublished.

Executive Summary - In two independent trials of an *in vitro* unscheduled DNA synthesis assay (MRID 46203329), primary rat hepatocyte cultures were exposed to Pinoxaden (Pinoxaden; 97.2% a.i., Batch # EZ005006) in acetone at concentrations of 0, 1.17, 2.34, 4.69, 9.38, 18.75, 37.5, 75, 150, 300, or 600 µg/mL for 19 hours (Trial 1) or 20 hours (Trial 2). The compound, 2-acetylaminofluorene, served as the positive control.

Pinoxaden was tested up to cytotoxic levels (≥300 µg/mL in both trials, determined by neutral red absorption). There were no marked increases observed in the mean grains per nucleus or mean NNG in either trial. The positive controls induced marked increases in mean grains per nucleus and mean NNG in both trials. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.**

The study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5550; OECD 482) for other genotoxic mutagenicity data.

46203335 Rumbeli, R. (2003) The Metabolism of (Phenyl-1-14C) NOA 407855 in the Rat: Final Report. Project Number: 046AM03. Unpublished study prepared by Syngenta Crop Protection, AG. 489 p.

Executive Summary: In a series of rat metabolism studies (MRIDs 46203333 through 46203336), [Phenyl-1-^{14}C]-Pinoxaden (>96% radiochemical purity) was suspended in aqueous 0.5% carboxymethylcellulose with 0.7% Tween 80 and 0.1% acetic acid and administered to Wistar rats by gavage. In the main mass balance studies (MRID 46203334), a single oral dose of [^{14}C] Pinoxaden was administered to 4 Wistar rats/sex/dose at nominal doses of 0.5 or 300 mg/kg bw. Urine, feces, and blood were collected over 7 days, and selected tissues were collected at termination. A biliary excretion study was performed on 5 bile duct cannulated rats/sex following a single oral low dose at 0.5 mg/kg bw. Urine, feces, and bile were collected over 48 hours, and the gastrointestinal tract (GIT) and carcass were analyzed for radioactive residues. Metabolites were determined in the urine, feces, and bile from rats in these studies (MRID 46203335). A tissue distribution time course study (MRID 46203336) was performed on the tissues from 3 rats/sex/time interval at 4 intervals after a single-dose, with the first interval corresponding to approximately Tmax of radioactivity in blood. In a repeat dose study (MRID 46203336), females rats were dosed daily with [^{14}C] Pinoxaden at 0.5 mg/kg bw/day for up to 14 days. Urine, feces, and blood samples were collected throughout dosing, and subgroups of 4 rats/interval were sacrificed to examine levels of radioactivity in tissues 24 hours after 1, 7 and 14 days of dosing and at 72 hours after the final dose. The metabolite profile in excreta was also examined qualitatively in selected urine and fecal samples.

Following administration of a single oral dose, radioactivity in blood increased rapidly in both sexes at both dose levels. At the low dose, Cmax was reached within 1 hour (0.15-0.17 ppm equiv.), and the initial half-life was approximately 1 hour in both sexes, and the terminal half-life was 6 hours in females. At the high dose, levels of radioactivity in blood essentially plateaued

between 1-12 hours post-dose, with Cmax of 26 and 18 ppm equiv. for males and females, respectively. The elimination half-life at the high dose was similar for both sexes (6–7 hours). Similar blood kinetics were also noted in the repeated low-dose group. Radioactivity levels in blood increased rapidly, and concentrations in blood at 2 hours following each daily dose were relatively constant over the entire dosing phase at 0.06-0.09 ppm equivalents. After the final 14th dose, radioactivity in blood declined rapidly, reaching values below the LOQ within 50 hours. The mean half-life in blood was calculated to be 7 hours in the repeated dose group. AUC values were calculated to be approximately 0.32 μg·h/g for the single low dose group and 342-456 μg·h/g for the single high dose group, with no apparent differences between the sexes. The ratio of the area under the curve values in blood for the high and low dose level was in the range of 1100 to 1500, whereas the dose level increased by a factor of 600, suggesting that some enterohepatic recirculation may occur at the high dose level.

Based on the above blood data and the high degree of renal and biliary excretion, the administered dose was rapidly and extensively absorbed by both sexes at both dose levels following a single oral dose. Excretion of the absorbed dose was also rapid and virtually complete, with >90% of the dose being excreted within 72 hours. Overall excretion accounted for 90-105% dose at both dose levels, with urine accounting for 59-77% of the dose and feces accounting for 25-28% of the dose. Excretion from bile-duct cannulated rats, confirmed that renal excretion (~77% dose) was the primary route of elimination followed by biliary (10-12% dose) and fecal (5-6% dose) excretion. Radioactivity remaining in the tissues and carcass at 7 days post-dose accounted for <2% dose, and expired air accounted for <0.01% dose. The total recovery of the administered dose was 91-105% dose.

Repeated dosing also had no affect on the route or rate of excretion. Throughout the 14-day dosing period, urine accounted for 64-79% of the daily dose and feces accounted for 16-26% of the daily dose. Over the entire study period, excreta accounted for >93% of the total dose (urine, 70% dose; feces, 22% dose), and residual radioactivity in tissues and carcass was <0.3% dose.

There was little or no apparent bioaccumulation of radioactivity following single or repeated dosing, and the relative distribution of radioactivity among tissues/organs was not affected by sex or dose level. Seven days following a single oral dose, concentrations of radioactivity in tissues were <LOQ in all tissues from the low dose group and were <LOQ in tissues from the high dose group, with the exceptions of liver and kidney (0.05-0.07 ppm) and blood and plasma (0.01-0.03 ppm equiv.). Following the concentration of radioactivity in tissues from single low and high dose rats beginning at ~Tmax indicated that the relative distribution of radioactivity among tissues was similar over time between the dose groups and sexes. With one minor exception, radioactivity levels were highest in liver and kidneys for both dose levels at all time points, and radioactivity in the remaining tissues were always below the levels observed in blood and plasma. Radioactivity peaked in the liver and kidneys between 1-2 hours post-dose for the low dose group (0.62-0.85 ppm equiv.) and at 8 hours post-dose for the high dose group (119-248 ppm equiv.). Half-lives of radioactivity in tissues typically ranged from 2-5 hours for the low dose group and 2-7 hours for the high dose group. The relative distribution of radioactivity in tissues was also similar between the single and repeated dose groups. At 24 hours following either 1, 7, or 14 days of dosing, radioactivity was highest in the liver and kidneys, followed by plasma and blood. Levels in the remaining tissues were always below the levels in blood (<0.003 ppm equiv.). After initially increasing, concentrations in blood and plasma were

relatively constant, and concentrations in liver and kidneys at 24 hours post-dose showed a low but steady increase from day 1 (0.008-0.013 ppm equiv.) through day 14 (0.017-0.029 ppm equiv.), but declined rapidly to <0.005 ppm equiv. within 3 days of the final dose.

The metabolite profile in excreta was similar regardless of dose level, sex, or duration of dosing. Following a single oral dose, the major metabolite identified in excreta was Metabolite M2 (62.6-91.0% dose). At both dose levels, Metabolite M2 was the major metabolite in both urine (50-73% dose) and feces (12-18% dose), and in bile-duct cannulated rats, its was also the major metabolite in bile (8.5-9.6% dose). The only other substantial metabolite was M4, which accounted for 5.0-15.6% of the dose in excreta. A total of 33 additional minor metabolites were also identified in seven HPLC fractions isolated from urine and feces of high dose rats; however, each of these fractions comprised ≤3.3% of the dose and included 2-7 metabolites. Parent test material was not detected in urine, feces, or bile. Although detailed qualitative and quantitative metabolite data were not provided for the repeated dose group, HPLC analyses of urine and fecal extracts from samples collected after the 1st and 14th dose showed the same relative distribution between Metabolites M2 and M4 as observed in the single-dose groups.

Based on the above profile, the metabolism of NOA 407855 in rats primarily involves the initial hydrolysis of the ester moiety to form Metabolite M2 (NOA 407854), which is then extensively excreted in the urine and feces. To a minor extent, Metabolite M2 is also further metabolized via hydroxylation, dealkylation, ring cleavage, ring formation, and conjugation into a wide variety of minor metabolites. The proposed pathway is also supported by the appended *in vitro* study, which indicates that NOA 407855 is rapidly hydrolyzed to M2 in rat plasma ($T_{½}$ = ~0.1 min) at concentrations up to 100 µM (~40 ppm).

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OPP 85-1] in rats.

46203337 Hassler, S. (2003) Absorption distribution and excretion of [Phenyl-1-^{14}C] NOA 407855 in the rabbit after oral administration. Health Assessment/Animal Metabolism, Syngenta Crop Protection AG, Basel, Switzerland. Laboratory Study Id.: Basel No.: 046AM08, July 24, 2003. Unpublished

Executive Summary: In a non-guideline rabbit metabolism study (MRIDs 46203337 and 46203338), a single oral dose of [Phenyl-1-^{14}C] NOA 407855 (Batch/lot # ILA-8.1B-5 and ILA-8.1C-1B; radiochemical purity ≥98.9%) was administered in aqueous 0.5% carboxymethylcellulose and 0.1% Tween 80 to female Chbb-HM rabbits (3/dose) via gavage at nominal dose levels of 0.5 and 300 mg/kg. Urine, feces, and blood samples were collected up to 168 hours after dosing. Metabolites in urine and feces were quantified and identified by HPLC, TLC, and LC/MS. Animals were sacrificed after 168 hours, and tissues were collected to determine of residual radioactivity.

Absorption and elimination of [^{14}C] NOA 407855 were rapid and essentially complete regardless of dose level. Maximum concentrations (C_{max}) in blood were attained within 0.5 hours at the low dose and within ~2 hours at the high dose. Half lives ($t_{½}$) for radioactivity in the blood were 3 and 12 hours for the low and high dose groups, and radioactivity in blood was non-detectable by 48 and 96 hours for the low and high dose groups.

The total recovery of the radioactive dose averaged 94.7-100.1% at 168 hours post-dose. The route of excretion was essentially independent of dose, although excretion was slightly retarded at the high dose compared to the low dose. Approximately 90% of the dose was excreted in the urine within 24 (low dose) or 48 (high dose) hours. An additional 4-7% dose was excreted in the feces within 48 hours. For both dose groups, concentrations of radioactivity remaining in the tissues were negligible by 168 hours post-dose and accounted for ≤0.1% of the dose. Quantifiable residues were detect in gall bladder and gastrointestinal (GI) tract for both the low dose group (0.0020-0.0025 ppm Eq.) and high dose group (1.66-1.69 ppm Eq.), and in the kidneys, liver, plasma, and blood (0.017-0.158 ppm) of the high dose group. However, radioactivity in the remaining tissues was below the limit of quantitation (LOQ).

Essentially all of the metabolites excreted in the urine and feces were identified (92.8-97.7% dose), and the metabolite profile was the same regardless of dose level. For both dose groups, Metabolite M2 (NOA 407854) was identified as the major component in both urine (88.6-91.0% dose) and feces (3.6-6.2% dose). Minor amounts of Metabolites M4 (0.4-0.6% dose), K4 (0.2% dose), M12 (0.2% dose) and K3 (0.1% dose) were also identified in urine and/or feces. Unidentified metabolites accounted for ≤0.6% dose.

In rabbits, the metabolism of NOA 407885 proceeds predominantly by hydrolysis of the ester linkage to form Metabolite M2 (NOA 407854), which is the major metabolite in urine and feces (92-97% dose). Minor secondary reactions include either: hydroxylation at the 4-methyl group of the phenyl moiety to yield M4 (excreted in urine and feces); or glucuronidation of M2 to form metabolite M12. The metabolic pathway in the rabbit is essentially identical to the rat.

This metabolism study in the rabbit is classified **acceptable/non-guideline**.

46203339 Briswalter, C. (2003) The metabolism of [Pyrazol-35-14C] NOA 407855 in the mouse: identification of metabolites in blood and excreta. RCC Ltd., Environmental Chemistry & Pharmanalytics, Itingen, Switzerland. Laboratory Study Id.: RCC No.: 851355, Syngenta No.: 046AM11, December 1, 2003. Unpublished.

Executive Summary: In a non-guideline mouse metabolism study (MRIDs 46203339 and 46224815), [pyrazol-3,5-^{14}C] NOA 407855 (≥97.6% radiochemical purity; Lots ILA-76.3B ILA-76.3C) was administered to 4 groups of male and female C57BL/10J$_f$/CD-1 mice as follows: (I) Group G1 was given either a single-dose or repeated daily dose of 1.4 mg/kg body-weight by gavage; (ii) Group G2 was administered either a single-dose or repeated daily dose of 140 mg/kg body-weight by gavage; (iii) Group G3 was fed at 10 ppm in the diet; and (iv) Group G4 was fed a 1000 ppm diet. The maximum duration of dosing in each group was for 18 days. Terminal blood samples were collected to determine a time course of the concentration of radioactivity in whole blood, and urine and feces were collected over 24 hours after varying time periods of dosing. The stated objectives of this study were to: (I) investigate the duration of dosing required to reach steady-state kinetics; (ii) compare systemic exposure following gavage or dietary dosing and determine any marked sex difference; (iii) compare blood and excreta metabolite profiles after single and multiple dosing to male and female mice; and (iv) resolve which metabolite should be analyzed during dietary studies.

Radioactivity levels in whole blood sampled at various post-dose intervals indicated that the gavage dose was rapidly absorbed (T_{max} = 0.5 hours) and eliminated regardless of the dose level or the duration of dosing. Absorption was slower for the dietary dosing groups (T_{max} = 8-12 hours), but elimination from the blood was rapid once mice were withdrawn from the treated diet. Concentrations in blood at T_{max} following 1, 7, 14, and 18 days of dietary dosing indicated that a steady state in blood levels was achieved within 18 days.

Although urinary excretion was typically higher than fecal excretion, there was no clear pattern in the distribution of excreted radioactivity between urine and feces based on sex, dosing group, or duration of dosing. Radioactivity in urine (including cage wash) varied from 26-83% of the excreted radioactivity and in feces from 17-74%.

Following oral administration of NOA 407855 to mice either by gavage or in the diet, the metabolite profiles in blood, urine and feces were qualitatively and quantitatively independent of sex, dose level, dosing method (gavage vs. dietary), dosing duration (single vs. multiple doses) and time of collection, although some quantitative variations were observed in feces.

Parent compound was not detected in blood, urine or feces. Metabolite M2 (NOA 407854) was the major component identified in all three matrices, accounting for ~67-93% of the extractable blood radioactivity, 69-89% of the total radioactivity in urine, and 35-75% of the radioactivity extractable from feces. Substantial amounts of Metabolite M4 were also detected in blood (2-11% extractable blood radioactivity), urine (5-14% of total radioactivity), and feces (12-41% of the extractable radioactivity). The remaining components detected in each matrix were minor (<8% of the sample radioactivity) and included five components in blood extracts, eight components in urine, and 8-11 components in fecal extracts.

The presence of Metabolites M2 and M4 in urine and feces were confirmed by LC/MS and LC/NMR analyses of fractions isolated from composited samples. These analyses also identified minor amounts (<3% sample radioactivity) of Metabolites M13, M21, M50, and M51 in urine and Metabolites M13, M19, M20, M22, M49, and M50 in fecal extracts.

Based on the metabolites identified in blood, urine and feces and their relative abundance, the metabolism of NOA 407855 in mice primarily involves hydrolysis of the ester moiety to form Metabolite M2, which is the primary component excreted in urine and feces. To a minor extent, Metabolite M2 may also undergo a number of secondary reactions to produce variety of minor metabolites. These secondary reactions include: hydroxylation, oxidation, hydrolysis, dealkylation, ring formation, and cleavage of the ether bond in the oxadiazepine moiety (See proposed pathway in Figure 1). Based on the metabolites identified, the metabolism of NOA 407855 in the mouse proceeds by the same major pathways as in the rat. This metabolism study in the mouse is classified **acceptable/non-guideline**.

46203340 Pinto, P.J. (2003) NOA 407855: Dietary toxicokinetic study in mice. Central Toxicology Laboratory, Cheshire, UK. Laboratory Study No.: KM1506, November 27, 2003. Unpublished

Executive Summary: In a non-guideline study designed to correlate the levels of Metabolite M2 (NOA 407854) in the blood with the ingestion of NOA 407855 in the diet, four groups of

C57Bl/10JfCD-1 mice (24/sex/dose group) were fed diets containing NOA 407855 (97.2% ai, Lot #EZ005006) for at least 39 consecutive days. Two groups were fed diets containing NOA 407855 at 1000 or 2500 ppm for the entire period; the third group was fed at 2500 ppm for 7 days, followed by 5000 ppm for at least 32 consecutive days; and the fourth group was fed at 2500 ppm for 7 days, followed by 5000 ppm for 14 days, and then 7000 ppm for at least 18 days. A fifth group of mice (3 or 4/sex) of the same source and strain served as controls for the duration of the study. All animals continued to receive their respective test diet up until the time of termination and blood sampling.

There were no effects of treatment on survival, clinical observations, or food consumption. At ≥ 5000 ppm, adjusted body-weights were decreased (decreased 3-12%; $p \leq 0.05$) in the males generally throughout treatment and in the females on days 2, 36 and 40. Overall body-weight gains, calculated by the reviewers, were decreased (decreased 21-50%; statistics not performed) in both sexes at this dose. Food utilization was decreased ($p \leq 0.05$) in the males for weeks 2-3 (decreased 64-65%) and in the females for the overall (weeks 1-5) study (decreased 39-68%).

Additionally at 7000 ppm, adjusted body-weights were decreased (decreased 7%; $p \leq 0.05$) in the females on day 29. Food utilization was decreased ($p <= 0.05$) in the females for weeks 4-5 (decreased 104%) and in the males for the overall (weeks 1-5) study (decreased 50%).

Concentrations of M2 in blood on Study days 40 and 41 averaged 1.7-2.3 mg/kg at 1000 mg/kg, 4.6-7.4 mg/kg at 2500 ppm, 11.8-12.7 mg/kg at 5000 ppm, and 17.0-20.8 mg/kg at 7000 ppm. Linear regression showed a direct correlation between the concentration of M2 in the blood and the concentration of the test material in the diet, with $R^2 = 0.96$ for females and 0.98 for males. There were no apparent differences in M2 blood concentrations between sexes or time of blood sampling at any dose.

This mouse study is classified **acceptable/non-guideline** and is adequate for the purposes for which it was intended.

46203342 Smith, A.D. (2003) NOA 407855: EC 100 formulation (A12303C): *In Vivo* dermal penetration study of NOA 407855 in the rat (NAFTA). Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study Id.: CTL No. UR0777, October 31, 2003. Unpublished

Executive Summary: In an *in vivo* dermal penetration study (MRID 46203342), [pyrazole-3, 5-^{14}C] NOA407855 (>95% radiochemical purity, lot/batch #EZ005006) was suspended in an emulsifiable concentrate (EC) formulation and applied neat or as aqueous dilutions to approximate exposure to the undiluted commercial formulation and to the dilute aqueous spray used in the field. The formulated test substance was administered to the shaved intact skin (10 cm^2) of 4 male Alpk:AP$_f$SD (Wistar-derived) rats/time point/dose at dose levels of 5 and 25 $\mu g/cm^2$ for the aqueous dilutions (1/200 and 1/40) and 400 $\mu g/cm^2$ for the neat EC formulation for a 4- or 10-hour exposure period. At the end of the exposure period, the skin of each rat was washed, and 4 rats/time point/dose were sacrificed for examination of dermal-absorption. A further 4 rats/dose were exposed for 10 hours and then retained for 24 hours after the skin was washed to determine further post-exposure absorption. In addition, *in vitro* studies were conducted using excised rat skin (MRID 46200343) and human skin (MRID 46200344) mounted

in a static diffusion cell apparatus to compare dermal-absorption. The dosing regimen used in the *in vitro* studies was the same as in the *in vivo* study, except that an additional dose level of 1000 μg/cm^2 was employed for human skin using the neat EC formulation. Absorption from excised skin samples was examined after 10- and 24-hour exposure durations, except at the 1000 μg/cm^2 dose level which used only a 10-hour exposure.

For the *in vivo* rat study, total recovery of the applied dose ranged from 84-96% for all dose groups.

For the neat EC formulation (**400 μg/cm^2**), 17% of the dose was absorbed after 4 hours and 30% dose after 10 hours, increasing to 36% dose over the following day (24 hours post-exposure). Regardless of exposure duration, 7% dose remained available in or on the skin for potential absorption, with 1.3-1.4% of the dose in the *stratum corneum*. At 24 hours post-exposure, the potentially absorbable dose declined to 5.3% dose, with 1.4% of the dose in the *stratum corneum*. Most of the absorbed radioactivity was excreted in the urine (including cage wash), accounting for approximately 30% of the applied dose (83% of the absorbed dose), and 3.3% dose was eliminated in the feces (9% of the absorbed dose). Excretion was virtually complete within 24 hours, with only 1.5% of the dose being recovered in the GI tract and carcass.

For the 1/40 aqueous spray dilution (**25 μg/cm^2**), absorption was markedly lower than for the EC formulation, with only 0.7 and 1.6% of the dose being absorbed by 4 and 10 hours, respectively. After a 10-hour exposure and washing, there was an increase in absorption up to 3.8% dose by 24 hours post-dose. Potentially absorbable radioactivity in or on the skin following washing accounted for 2.6-3.1% of the dose at all sampling intervals and was primarily associated with the *stratum corneum* (2.0-2.3% dose). As with the high-dose group, most of the absorbed radioactivity was excreted within 24 hours in the urine (66% of absorbed dose) and feces (11% of absorbed dose).

For the 1/200 aqueous spray dilution (**5 μg/cm^2**), absorption was lower than for the EC formulation but greater than for the 25 μg/cm^2 group. The absorbed dose accounted for 4% of the dose after a 4-hour exposure and 14% dose after a 10-hour exposure, increasing to 17% dose the day after the 10-hour exposure. Potentially absorbable radioactivity in or on the skin following washing accounted for 11.3 and 13.7% of the dose following the 4- and 10-hour exposures, respectively, and declined to 7.0% of the dose 24 hours following the 10-hour exposure. At each sampling interval the majority of the potentially absorbable dose was associated with the *stratum corneum* (4.8-7.8% dose) rather than the epidermis (2.2-5.9% dose).

Again, most of the absorbed radioactivity was excreted within 24 hours in the urine (62% of absorbed dose) and feces (15% of absorbed dose).

For the *in vitro* studies using excised rat and human skin, total recovery of the applied dose ranged from 94-104% for all dose groups at both exposure intervals.

As in the *in vivo* study, absorption from **excised rat skin** was higher for the neat EC formulation (400 μg/cm^2) than for either of the 1/200 or 1/40 aqueous dilutions (5 and 25 μg/cm^2, respectively). Following a 10-hour exposure, 40.3% of the applied dose from the EC formulation was absorbed compared to 34.1 and 25.0% of the applied dose from aqueous dilutions (5 and 25

$\mu g/cm^2$). After 24 hours of exposure, absorption rose to 65.5% dose for the EC formulation and 49.0 and 44.7% dose for the aqueous dilutions. Regardless of exposure duration, potentially absorbable radioactivity remaining on the skin accounted for 8.8-11.8% dose for the neat EC formulation, 12.1-12.9% dose for the 1/40 aqueous dilution, and 18.5-20.6% dose for the 1/200 aqueous dilution.

For excised **human skin**, absorption of radioactivity was minimal regardless of the dosing vehicle and dose level. Absorption accounted for 0.34-1.55% of the applied dose after a 10-hour exposure at doses from 5-1000 $\mu g/cm^2$ and 0.36-1.84% of the applied dose after a 24-hour exposure at doses from 5-400 $\mu g/cm^2$. Potentially absorbable radioactivity remaining in or on the skin (stratum corneum and epidermis) accounted for 2.42-3.61% dose in the ≥ 25 $\mu g/cm^2$ dose groups and 8.49-8.80% dose in the 5 $\mu g/cm^2$ dose group. Thus, in the *in vitro* studies, absorption was considerably higher in rat skin than in human skin. Additionally, absorption of the test substance in the *in vivo* rat study was comparable to the absorption in the *in vitro* study with rat skin. Therefore, the data may suggest that *in vivo* absorption in humans would be considerably lower than in the rat.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD Draft Guidance Document for the Conduct of Skin Absorption Studies, No. 28, Dec. 2000 & OECD Guidance for the Testing of Chemicals - Draft New Guideline 428: Skin Absorption: *In vitro* Method, Dec. 2000 & OECD Guideline for the Testing of Chemicals - Draft New Guideline 427: Skin Absorption: *In vivo* Method, Dec. 2000) for a dermal penetration study in rats.

46224808 Gerspach, R. (2003) 18-month carcinogenicity study in mice (gavage) (includes final report amendment no. 1 replaces EPA MRID 46203313). RCC Ltd., Toxicology, Stein, Switzerland. Laboratory Study No.: 20011039, December 12, 2003. Unpublished.

Executive Summary: In a carcinogenicity study (MRIDs 46224808, 46224807, and 46203310), NOA- 407855 (Pinoxaden; 97.2% a.i.; Batch # EZ005006) in 0.5% (w/v) carboxymethylcellulose, 0.1% (w/v) aqueous Tween 80 in distilled water was administered by daily gavage at a dose volume of 10 mL/kg bw to Crl:CD-1(ICR)BR mice (70 /sex/dose) at doses of 0, 5, 40, 300, or 750 mg/kg bw/day for up to 78 weeks.

No treatment-related effects were observed on food consumption.

Survival was decreased in males in the 40 (57%), 300 (47%) and 750 mg/kg/day (47%) when compared to controls (83%) and the 5 mg/kg/day (79%) groups.

At ≥ 300 mg/kg bw/day, body-weight in females decreased ($p \leq 0.05$) by 6-23% (at weeks 77 and 78 at 300 mg/kg bw/day and generally during weeks 23-78 at 750 mg/kg bw/day). A decrease ($p \leq 0.01$) was also observed in overall (weeks 1-78) body-weight gain in the females (decreased 38-84%). Overall (weeks 1-77) food efficiency was decreased ($p \leq 0.05$) in both sexes (0.5-0.9% treated vs 1.1-1.5% controls; not reported for 750 mg/kg bw/day females). Relative to body liver weight was increased ($p \leq 0.05$) in both sexes (55.8-71.4% treated vs 49.0-50.1% controls). Minimal to marked glycogen deposition was observed (# affected/70) in the liver of the males

(46-51 treated vs 33 controls) and females (55-57 treated vs 50 controls), and severity increased with dose. Moderate to marked glycogen deposition was observed in the liver of the males (4-8 treated vs 0 controls) and females (8-21 treated vs 1 control).

At 750 mg/kg bw/day, the incidence of tonic convulsions in males, piloerection in both sexes, and hunched posture in females were increased. In males, body-weight was decreased ($p \leq 0.05$) generally during week 35-78, and in body-weight gain at weeks 1-13, 1-27, 1-51, and 1-78, and the decrease grew with time. Water consumption was increased ($p \leq 0.05$) generally throughout the study in the males and females. Absolute liver weight was increased ($p \leq 0.01$) in both sexes. The relative to body kidney weight was increased ($p \leq 0.01$) in the females, and minimal to moderate tubular atrophy and casts were increased. Glycogen deposition was observed in the liver of the ≥300 mg/kg bw/day males (minimal to marked in 46-51 treated mice vs minimal to slight in 33 control mice) and the ≥300 mg/kg bw/day females (minimal to marked in 55-57 treated mice vs minimal to moderate in 50 control mice). In the kidney of the 750 mg/kg bw/day females, the incidence of minimal to slight tubular atrophy was increased (19 treated vs 8 controls), as was minimal to moderate tubular casts (38 treated vs 25 controls).

Minimal to marked congestion was observed in the liver, kidney, and lung in the ≥40 mg/kg bw/day males (11-31 treated vs 2-7 controls) and ≥300 mg/kg bw/day females (8-15 treated vs 0-4 controls). Slight to moderate congestion was also observed in the adrenal gland in the 750 mg/kg bw/day males (8 treated vs 0 controls). There was a dose-related increase in the incidence of hyalinosis of the lung in males in the 40, 300 and 750 mg/kg/day groups (6, 11 and 29%, respectively; control: 3%) and in females in the 750 mg/kg/day group (27%; control: 7%). In addition, the severity of the hyalinosis increased with dose in males in the 40, 300 and 750 mg/kg/day groups and in females in the 300 and 750 mg/kg/day groups. There was also a dose-related increase in "pus" in the nose in males in the 300 and 750 mg/kg/day groups when compared to controls (9, 11 and 0%, respectively). Females in the 300 and 750 mg/kg/day groups had increase in an inflammatory response in the nose: pus (11 and 41%, respectively; control 0%), inflammatory cell infiltration (39 and 53%, respectively; control: 10%) and purulent infiltration (3 and 16%, respectively; controls: 0%).

A NOAEL/LOAEL could not be determined. The study could not be interpreted due to gavage errors and lung involvement.

At the doses tested, there were increases in the incidence of bronchiolo-alveolar carcinomas in the 40 and 300 mg/kg bw/day males (11-13% treated vs 4% controls) and combined adenomas and carcinomas in the 300 mg/kg bw/day males (26% treated vs 16% controls). In the 750 mg/kg bw/day males, positive trends ($p \leq 0.05$) were observed in the incidence of adenomas (14% treated vs 11% controls), carcinomas (7% treated vs 4% controls), and combined adenomas and carcinomas (17% treated vs 16% controls). The incidences of bronchiolo-alveolar adenomas, carcinomas, and combined adenomas and carcinomas at 750 mg/kg bw/day were within the historical control range, and the incidence of carcinomas only slightly exceeded the historical control range at 300 mg/kg bw/day (13% treated vs 2-12% historical controls). The incidence of these lesions in the females was similar to controls tumor incidence when compared to controls. Dosing was considered adequate based on decreased survival in males, and decreased food efficiency, body-weight and body-weight gain, and pathological effects in the lungs, liver and kidneys in both sexes.

It was the general consensus of the Cancer Peer Review Committee that the study was not interpretable and not useful for risk assessment. There was increased mortality at 40, 300 and 750 mg/kg/day in males. The occurrence of gavage error together with lung involvement confounded the results of the study.

This study is classified as **Unacceptable/guideline** and does not satisfy the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice. The study can not be upgraded.

46224809 Bachmann, M. (2003) 24-month carcinogenicity and chronic toxicity study in rats (gavage) (includes final report amendments numbers 1 and 2 replaces EPA MRID 46203312). RCC Ltd. Toxicology, Stein, Switzerland. Laboratory Study Id.: RCC No. 20001124, September 10, 2003. Unpublished.

Executive Summary - In this combined chronic toxicity/carcinogenicity study (MRID 46224809), NOA 407855 technical (Pinoxaden; 97.2% a.i.; Batch No.: EZ005006) in 0.5% carboxymethylcellulose, 0.1 % Tween 80 in distilled water was administered for 24 months by daily gavage to 80 HanIbm:WIST rats/sex/dose at doses of 0, 1, 10, 100, 250, or 500 mg/kg/day in a volume of 10 mL/kg bw. Additionally, 10 rats/sex/dose were treated similarly and sacrificed at 12 months.

No treatment-related effects were observed on food consumption or ophthalmoscopic examination. No treatment-related adverse-effects were observed on hematology.

Several indications of systemic toxicity were observed. At ≥250 mg/kg/day, survival was decreased in males, and the incidences of hunched posture and piloerection were increased. In the ≥250 mg/kg/day groups, body-weights and body-weight gains were decreased, and water consumption was increased. The surviving 500 mg/kg/day males were terminated at week 61 due to continuously increasing spontaneous death. Nephrotoxicity was indicated by numerous clinical and pathological parameters. Decreased in serum glucose was observed in both sexes at doses 250 and 500 mg/kg/day. At ≥250 mg/kg/day, the following evidence supported nephrotoxicity: (I) increased serum urea and creatinine in the males; (ii) increased urine volume in both sexes generally throughout treatment; (iii) decreased relative (to body) kidney weights in the females at week 105; (iv) increased incidence of surface granulation in the kidney at interim (males only) and terminal sacrifices (both sexes); (v) increases in incidence and severity of chronic nephropathy in males at week 105; and (vi) increases in incidence and severity of renal pelvis dilatation in females at week 105. At 500 mg/kg/day, the following evidence supported nephrotoxicity: (I) increased serum urea and creatinine in the females; (ii) increased urinary ketones in the females; (iii) increased epithelial cells in the urine of both sexes; (iv) increased urinary casts in the females; (v) increased absolute and relative kidney weights in males at week 53; (vi) increased incidence of surface granulation in the kidney of the females at week 53; and (vii) increased incidences of chronic nephropathy, renal tubular vacuolation, and renal cysts in the females at week 105. At week 105 in the 250 mg/kg/day males, increases were observed in incidence and/or severity of fibrous osteodystrophy and parathyroid hyperplasia, accompanied by increased relative thyroid and parathyroid weight. The Sponsor suggested that these were secondary findings due to severe renal damage.

Additional observations were made in the females at the terminal sacrifice. Grossly, an increased incidence of thickened small intestine was observed at ≥250 mg/kg/day. Epithelial thickening of the small intestine was observed microscopically at 500 mg/kg/day, as was ulceration of the large intestine. A cortical fatty change was observed in the adrenal glands at 500 mg/kg/day, accompanied by an increased relative adrenal weight. Mast cell infiltration of the mesenteric lymph node at ≥ 250 mg/kg/day and white pulp atrophy in the spleen at 500 mg/kg/day were also observed.

The LOAEL is 250 mg/kg bw/day, based on mortality, clinical signs, and increased serum urea and creatinine in males, and decreased body-weights and body-weight gains, increased water consumption and incidence of urinalysis findings, kidney surface granulation, and microscopic renal lesions in both sexes. The NOAEL is 100 mg/kg bw/day.

The incidence of leiomyosarcoma (2 in the stomach; 1 in the body cavity) was increased in the 250 mg/kg/day males (4%) compared to concurrent (0%) and historical (0-2%) controls. Leiomyosarcomas were also observed in the spleen of one male in each of the 1 and 10 mg/kg/day groups, in the stomach of one female in the 10 mg/kg/day group and in the uterus of a female control rat. Additionally, a leiomyoma was observed in the small intestine of one male in the 100 mg/kg/day group and in the uterus of a female control rat. The incidence of other tumors occurred in only a single animal, was similar to concurrent controls, and/or was within the historical control range. Dosing was considered adequate based on decreased survival, body-weight and body-weight gain, and nephrotoxicity, as well as other indications of toxicity.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

46448801 Pinto, P. (2004) NOA 407855 Tech.; 80-week carcinogenicity study in mice (includes final report amendment 1). Central Toxicology Laboratory, Alderly Park, Macclesfield, Cheshire, UK. Laboratory Study No.: CTL Number PM1280, December 22, 2004. Unpublished.

Executive Summary: In a carcinogenicity study (MRIDs 46448801), NOA- 407855 (Pinoxaden; 97.2% a.i.; Batch # EZ005006) was administered in the diet to C57BL/10J,CD-1 mice (50 /sex/dose) at doses of 0, 150, 500, 1500 or 4000 ppm (representing mean dosages of: 0, 16.3, 60.7, 181.2 and 573.7 mg/kg bw/day, respectively, in male mice; and 0, 20.2, 75.7, 216.5 and 706.4 mg/kg bw/day, respectively, in female mice for up to 80 weeks.

Animals in the 4000 ppm group were terminated at week 40 due to what the sponsor considered to be excessive decreases in body-weight gain in males and females (31 and 33%, respectively). Food consumption was statistically significantly increased in males fed 4000 ppm in the diet from weeks 11 to 16 and weeks 28-36, and in females in fed 4000 ppm in week 11. Food utilization was significantly decreased in males and females fed 4000 ppm in the diet from weeks 1-4 (14 and 23%, respectively), 9-13 (25 and 35%, respectively) and generally during the whole time period of rapid growth (1-13 weeks/18 and 27%, respectively).

The mean body-weights of males and females in the 1500 ppm group were statistically

significantly decreased beginning at week 2 when compared to controls. Males in the 1500 ppm group reached a maximum decrease of 10% relative to controls at week 55 and 63. Whereas, females reached their maximum decrease of 9% relative to controls at week 81. Mean body-weight gain was similar across dose levels for males. Female body-weight gain was variable, but was decreased 18% in females in the 1500 ppm group when compared to controls from weeks 1-81. Food utilization was decreased in males between weeks 1-4 (10%) and weeks 1-13 (20%). There was a slight increase in the number of females in the 1500 ppm group (3/50) with pale livers or pale spots/areas in the liver (1/50) compared to females in the 0 (1/50), 150 (1/50) and 500 (0/50) ppm groups. There was an increase in the incidence of mononuclear cell infiltration in the pancreas of females in the 1500 ppm group (16/50; 32%) when compared to the control (8/49; 16%), 50 ppm (8/48; 17%) and 500 ppm (9/48; 19%) groups.

Females in the 500 ppm had a decrease of approximately 5% in body-weight when compared to controls beginning at week 35.

The LOAEL was not determined. The NOAEL is 1500 ppm (181.2 mg/kg/day and 216.5 mg/kg bw/day, respectively) in males and females.

This study is classified as **Unacceptable/guideline** and does not satisfy the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice. Dosing was inadequate. The study can not be upgraded.

Metabolite SYN 502836 (M6)

46203238 Brammer, A. (2003) SYN 502836 (Metabolite of NOA 407855): 90 Day Dietary Toxicity Study in Rats (Includes Report Amendment 001): Final Report. Project Number: PR1258, TL/PR1258/REG/AM/002, CTL/PR1258/REG/REPT. Unpublished study prepared by Central Toxicology Lab (Syngenta). 939 p.

Executive Summary - In this subchronic oral toxicity study (MRIDs 46203238 and 46203232), 12 Alpk:AP$_f$SD rats/sex/dose were exposed to SYN 502836 (metabolite of Pinoxaden; 99% a.i.; Batch #: KI-6513/10 M) in the diet at concentrations of 0, 300, 3000, or 12,000 ppm nominally (equivalent to 0/0, 23.9/26.8, 246.8/266.4, and 977.5/1034.9 mg/kg/day in males/females) for up to 90 days.

No treatment-related effects were observed on mortality, clinical signs, functional observational battery, motor activity tests, body-weight, food consumption, food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, organ weights, or necropsy.

Severity of proteinuria increased in all treated males. The following microscopic lesions were observed (minimal severity, # affected/12 treated vs #/12 controls) at 12,000 ppm: (I) hepatitis in males (8 vs 4); (ii) renal tubular basophilia in females (6 vs 3); and (iii) interstitial mononuclear cell infiltration in the kidney in females (4 vs 0). Toxicity was not corroborated in the liver or kidney. The parent can cause hepatic and renal toxicity; therefore, effects in the liver and kidney are considered equivocal.

The LOAEL was not observed. The NOAEL is 12,000 ppm (equivalent to 977.5/1034.9

mg/kg/day in males/females; approximately the limit dose).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

46203316 Callander, R. (2003) SYN 502836 (Metabolite of NOA 407855): Bacterial Mutation Assay in S. typhimurium and E. coli: Final Report. Project Number: YV6182. Unpublished study prepared by Central Toxicology Lab (Syngenta). 31 p.

Executive Summary - In two independent reverse gene mutation assays in bacteria (MRID 46203316), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strains WP2 *uvr*A (pKM101) and WP2 (pKM101) were exposed to SYN 502836 (a metabolite of NOA 407855 tech.; Pinoxaden; 99% a.i., Batch # KI 6513/3M) in dimethylsulfoxide (DMSO) at concentrations of 100, 200, 500, 1000, 2500, or 5000 µg/plate in the presence and absence of mammalian metabolic activation (+/-S9). The standard plate incorporation method was performed in Trial 1 (+/-S9) and Trial 2 (-S9), while a pre-incubation step was added in Trial 2 (+S9). Standard strain-specific mutagens served as positive controls.

SYN 502836 was tested up to the limit dose (5000 µg/plate). Cytotoxicity (as indicated by reduction in number of revertants) was limited to Trial 2 at 5000 µg/plate in strains TA100 (+/-S9), TA1535 (-S9), TA1537 (-S9), and WP2 *uvr*A (pKM101, +/-S9); and at ≥2500 µg/plate in strain WP2 (pKM101, -S9). No marked increases in the number of revertants were observed at any concentration in any strain in either trial. The positive controls induced marked increases in revertant colonies compared to controls in both trials. **There was no evidence of induced mutant colonies over background.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

Metabolite SYN 505887 (M10)

46224810 Callander, R. (2003) SYN 505887 (Metabolite of NOA 407855): Bacterial Mutation Assay in S. Typhimurium and E. Coli: Final Report. Project Number: YV6549. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 31 p.

Executive Summary - In two independent reverse gene mutation assays in bacteria (MRID 46224810), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strains WP2 *uvr*A (pKM101) and WP2 (pKM101) were exposed to SYN 505887 (a metabolite of NOA 407855 tech.; [Pinoxaden]; 99% a.i., Batch # KI 6721/4) in dimethylsulfoxide (DMSO) at concentrations of 100, 200, 500, 1000, 2500, or 5000 µg/plate in the presence and absence of mammalian metabolic activation (+/-S9). The standard plate incorporation method was performed in Trial 1 (+/-S9) and Trial 2 (-S9), while a pre-incubation step was added in Trial 2 (+S9). To clarify the results obtained in Trials 1 and 2, a third plate incorporation assay (+S9) was performed using *S. typhimurium* strain TA1535 only. Standard strain-specific mutagens served as positive controls.

SYN 505887 was tested up to the limit dose (5000 µg/plate). Cytotoxicity (as indicated by reduction in number of revertants) was limited to strain TA98 at ≥1000 µg/plate (+S9) in Trial 1. Increases (≥2x the solvent control) in the number of revertants were observed in strain TA1535 at 100 and 2500 µg/plate in Trial 1 (+S9) and at 5000 µg/plate in Trial 3 (+S9), but were not observed in Trial 2. These findings were not considered to be treatment-related, because they were not reproducible. No marked increases in the number of revertants were observed in any other strain under any test condition in either trial. The condition of the background lawn was not reported for any trial. The positive controls induced marked increases in revertant colonies compared to controls in all trials. **There was no evidence of induced mutant colonies over background.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

46224812 Fox, V. (2003) SYN 505887 (Metabolite of NOA 407855): *In vitro* Cytogenetic Assay in Human Lymphocytes: Final Report. Project Number: SV1214. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 31 p.

Executive Summary - In two independent trials of a mammalian cell cytogenetics assay (chromosome aberration; MRID 46224812), lymphocyte cultures were prepared from human peripheral blood and exposed to SYN 505887 (a metabolite of NOA 407855 tech.; Pinoxaden; 99% a.i., Batch # KI 6721/4) in dimethylsulfoxide (DMSO) at concentrations of 10, 50, 100, 250, 500, 750, 1000, 1500, 2500, and 3484 µg/mL for 3 hours with a 17 hour recovery period (Trial 1, +/-S9); 100, 250, 500, 750, 1000, 1500, 2500, and 3484 µg/mL for 20 hours with no recovery period (Trial 2, -S9); or 250, 1500, 2500, and 3484 µg/mL for 3 hours with a 17 hour recovery period (Trial 2, +S9).

SYN 505887 was tested up to 3484 µg/mL (limit dose, 10 mM). Cytotoxicity (as evidenced by reduced mitotic index) was noted in Trial 1 at 3484 µg/mL (-S9) and ≥1500 µg/mL (+S9), and in Trial 2 at ≥750 µg/mL (-S9). There were no treatment-related increases in the percent aberrant cells (excluding gaps) noted in either trial in the presence or absence of S9. The positive controls induced the appropriate response in both trials in the presence and absence of S9. **There was no evidence of chromosome aberrations induced over background in the presence or absence of S9-activation.**

This study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

46224813 Fox, V. (2004) SYN 505887 (Metabolite of NOA 407855): Rat Bone Marrow Micronucleus Test: Final Report. Project Number: SR1236. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 25 p.

Executive Summary - In a bone marrow micronucleus assay (MRID 46224813), 5 non-fasted male Alpk AP$_f$SD rats/dose/sacrifice time were treated once via gavage (20 mL/kg) with SYN 505887 (a metabolite of NOA 407855 [Pinoxaden]; 99% a.i., Batch # KI 6721/4) in 0.5% (w/v)

aqueous carboxymethylcellulose (CMC) at doses of 0 or 2000 mg/kg bw. Bone marrow cells were harvested at 24 or 48 hours post-dosing. Cyclophosphamide (20 mg/kg) served as the positive control.

SYN 505887 was tested up to the limit dose (2000 mg/kg); however, no evidence of bone marrow toxicity (decreased % PCE) was observed at the 24 or 48 hour sampling times. No clinical signs of toxicity were noted in any animal. No abnormalities were observed in the internal organs of the treated animals. No significant increase in micronucleated polychromatic erythrocytes (MPCEs) was observed at either 24 or 48 hours post-dosing. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirement (OPPTS 870.5395; OECD 474) for *in vivo* cytogenetic mutagenicity data.

46224814 Clay, P. (2004) SYN 505887 (Metabolite of NOA 407855): *in vivo* Rat Liver Unscheduled DNA Synthesis Assay: Final Report. Project Number: SR1212. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 27 p.

Executive Summary - In an *in vitro/in vivo* unscheduled DNA synthesis assay (MRID 46224814), rat hepatocyte cultures were prepared from 3 male (Alpk:AP$_f$SD) rats/sacrifice time that were treated orally (gavage, 20 mL/kg) once with SYN 505887 (a metabolite of NOA 407855 tech.[Pinoxaden]; 99% a.i., Batch # KI 6721/4) in 0.5% aqueous carboxymethylcellulose at a dose of 2000 mg/kg (limit dose). Hepatocytes were harvested after 2 or 16 hours of exposure. Additionally, 2 rats/sacrifice time were similarly treated with the vehicle or positive control (–nitrosodimethylamine).

SYN 505887 was tested up to the limit dose (2000 mg/kg). There were no adverse clinical signs of toxicity in the treated animals or evidence of excessive cytotoxicity in any of the cultures. There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG $\geq$5) at 2 or 16 hours post-dosing compared to controls. The positive control induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.**

The study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5550; OECD 486) for other genotoxic mutagenicity data Although, the dosing formulation was not analyzed for the amount of test substance, this is not considered to be a major deficiency that would have altered the results of the study, since the limit dose was tested and the testing laboratory adheres to GLP regulations, and has a QA unit.

Metabolite 447204(M3)

46203240 Twomey, K. (2003) NOA 447204 (Metabolite of NOA 407855): 90 Day Dietary Toxicity Study in Rats: Final Report. Project Number: PR1253, CTL/PR1253/REG/REPT. Unpublished study prepared by Central Toxicology Lab (Syngenta). 973 p.

Executive Summary - In this subchronic oral toxicity study (MRIDs 46203240, 46203231, and 46203233), 12 Alpk:AP$_f$SD rats/sex/dose were exposed to NOA 447204 (metabolite of Pinoxaden; 99% a.i.; Batch #: KI 6385/17) in the diet for up to 90 days at concentrations of 0, 150, 1000, or 6000 ppm nominally (equivalent to 0/0, 15.0/15.2, 99.2/98.8, and 600.6/645.4 mg/kg bw/day in males/females).

No treatment-related effects were observed on mortality, clinical signs, food consumption, ophthalmoscopic examination, or hematology.

In the 6000 ppm group, body-weights were decreased throughout the study, except week 3 (males only). Decreased ($p \leq 0.05$) body-weight was observed in males at days 2, 3, and 6 (decreased 2-3%) and in females at day 2 and weeks 3-14 (decreased 2-11%). Overall (weeks 1-14) body-weight gains were decreased in both sexes (decreased 10-19%). Decreased ($p \leq 0.05$) food efficiency was observed in the males at weeks 1-4 (decreased 9%) and 5-8 (decreased 23%). Decreased (NS) food efficiency was observed throughout the study in the females. Decreased ($p \leq 0.05$) overall (weeks 1-13) food efficiency was observed in males (decreased 9%) and females (decreased 22%). Water consumption was decreased throughout the study in the females and was statistically different ($p \leq 0.05$) at weeks 3, 5, 12, and 13 (decreased 23-32%).

At 6000 ppm, there were indications of hepatotoxicity. Increased ($p \leq 0.05$) gamma-glutamyl transferase was observed in males (incr 13%) and females (incr 53%). Decreased ($p \leq 0.01$) triglycerides were observed in males (decreased 27%). Increased ($p \leq 0.01$) cholesterol was observed in the females (incr 21%). Increased ($p \leq 0.05$) absolute and adjusted (for terminal body-weight) liver weights were observed in both sexes (incr 22-35%). Two males (n=12) had enlarged livers (vs 0 in controls and other doses). Minimal to moderate panlobular reduced glycogen/increased eosinophilia in the liver was observed (n=12) in the males (12 treated vs 0 controls) and in the females (11 treated vs 0 controls; slight severity).

In the 6000 ppm males, there were indications of nephrotoxicity. Increased severity of proteinuria and incidence and severity of ketonuria (9/12 treated vs 4/12 controls) were observed. Increased ($p \leq 0.05$) absolute and adjusted kidney weights were observed (incr 11-17%). Additionally, minimal chronic progressive nephropathy was observed (6/12 treated vs 2/12 controls).

The LOAEL is 6000 ppm (equivalent to 600.6/645.4 mg/kg bw/day in males/females), based on decreased body-weight and body-weight gain and food efficiency in both sexes, and evidence of hepatotoxicity in both sexes and nephrotoxicity in males. The NOAEL is 1000 ppm (equivalent to 99.2/98.8 mg/kg bw/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

46203315 Callander, R. (2003) NOA 447204, Metabolite of Pinoxaden: Bacterial Mutation Assay in S. Typhimurium and E. coli: Final Report. Project Number: YV6168. Unpublished study prepared by Central Toxicology Lab (Syngenta). 32 p.

Executive Summary - In two independent reverse gene mutation assays in bacteria (MRID

46203315), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strains WP2 *uvr*A (pKM101) and WP2 (pKM101) were exposed to NOA 447204 (a metabolite of Pinoxaden tech.; Pinoxaden; 99% a.i., Batch # KI 6385/17) in dimethylsulfoxide (DMSO) at concentrations of 100, 200, 500, 1000, 2500, or 5000 µg/plate in the presence and absence of mammalian metabolic activation (+/-S9). The standard plate incorporation method was performed in Trial 1 (+/-S9) and Trial 2 (-S9), while a pre-incubation step was added in Trial 2 (+S9). To clarify the results obtained in Trials 1 and 2, a third plate incorporation assay (±S9) was performed using *S. typhimurium* strain TA1535 only. Standard strain-specific mutagens served as positive controls.

NOA 447204 was tested up to the limit dose (5000 µg/plate). Cytotoxicity (as indicated by reduction in number of revertants) was limited to strains TA98 and WP2 (pKM101) at >=2500 µg/plate (-S9) in Trial 1, and strain TA1535 at 5000 µg/plate (+S9) in the repeat trial. No marked increases in the number of revertants were observed at any concentration in any strain in any trial. The condition of the background lawn was not reported for any trial. The positive controls induced marked increases in revertant colonies compared to controls in all trials. **There was no evidence of induced mutant colonies over background.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

46203323 Fox, V. (2003) NOA 447204 (Metabolite of Pinoxaden): *In vitro* Cytogenetic Assay in Human Lymphocytes: Final Report. Project Number: SV1135. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 32 p.

Executive Summary - In two independent trials of a mammalian cell cytogenetics assay (chromosome aberration; MRID 46203323), lymphocyte cultures were prepared from human peripheral blood and exposed to NOA 447204 (a metabolite of Pinoxaden tech.; Pinoxaden; 99±2% a.i.; Batch # KI 6385/17) in dimethylsulfoxide (DMSO) at concentrations of 50, 100, 250, 500, 750, 1000, 1500, 2000, 2500, 3000, and 3324 µg/mL for either 3 hours with a 17 hour recovery period (Trial 1, +/-S9 and Trial 2, +S9) or 20 hours with no recovery period (Trial 2, -S9).

NOA 447204 was tested up to cytotoxic concentrations (1500 µg/mL, +S9 and ≥500 µg/mL, -S9). At 1500 µg/mL, NOA 447204 induced increased ($p \leq 0.05$) aberration frequencies (excluding gaps) in the presence of S9 in Trials 1 and 2 (4.5-8.67% treated vs 1.0% solvent control), and in the absence of S9 in Trial 1 (6.5% treated vs 2.0% solvent control) after a 3 hour treatment period and a 17 hour recovery period. The significant increases observed equaled or exceeded the upper limit of the historical control ranges. The positive controls induced the appropriate response in all assays. **There was evidence of chromosome aberrations induced over background in the presence and absence of S9-activation.**

This study is classified as **Acceptable/Guideline** and not satisfies the Guideline requirement (OPPTS 870.5375, OECD 473) for *in vitro* mutagenicity (chromosome aberration) data.

46203326 Fox, V. (2003) NOA 447204 (Metabolite of Pinoxaden): *in vivo* Rat Liver Unscheduled DNA Synthesis Assay: Final Report. Project Number: SR1189.

Unpublished study prepared by Central Toxicology Lab. (Syngenta). 26 p.

Executive Summary - In an *in vitro/in vivo* unscheduled DNA synthesis assay (MRID 46203326), rat hepatocyte cultures were prepared from 3 male (Alpk:AP$_f$SD) rats/dose/sacrifice time that were treated orally (gavage, 10 mL/kg) once with NOA 447204 (a metabolite of Pinoxaden tech.; Pinoxaden; 99% a.i.; Batch # KI 6385/17) in dried corn oil at concentrations of 625 or 1250 mg/kg. Hepatocytes were harvested after 2 or 16 hours of exposure. Additionally, 2 rats/sacrifice time were treated with the vehicle or positive control (–nitrosodimethylamine).

NOA 447204 was tested up to the maximum tolerated dose (MTD, 1250 mg/kg). There were no clinical signs of toxicity in the treated animals or evidence of excessive cytotoxicity in any of the cultures. There were no marked increases observed in mean net nuclear grains (NNG) or percent cells in repair (NNG ≥5) at 2 or 16 hours post-dosing compared to controls. The positive control induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.**

The study is classified as **Acceptable/Guideline** and satisfies the Guideline requirement (OPPTS 870.5550; OECD 486) for other genotoxic mutagenicity data. Although, the dosing formulations were not analyzed for the amount of test substance, this is not considered to be a major deficiency that would have altered the results of the study, since the test substance was tested at the MTD the testing laboratory adheres to GLP regulations, and has a QA unit.

46203328 Fox, V. (2003) NOA 447204 (Metabolite of Pinoxaden): Mouse Bone Marrow Micronucleus Test: Final Report. Project Number: SM1188. Unpublished study prepared by Central Toxicology Lab. (Syngenta). 27 p.

Executive Summary - In a bone marrow micronucleus assay (MRID 46203328), 5 non-fasted male CD-1 mice/dose/sacrifice time were treated once via gavage (10 mL/kg) with NOA 447204 (a metabolite of Pinoxaden [Pinoxaden]; 99% a.i., Batch # KI 6385/17) in dried corn oil at doses of 0, 200, 400, or 800 mg/kg bw. Bone marrow cells were harvested at 24 (all doses) or 48 hours (vehicle and 800 mg/kg only) post-dosing. Cyclophosphamide (65 mg/kg) served as the positive control.

NOA 447204 was tested up to the limit toxicity (800 mg/kg). Clinical signs of toxicity (decreased activity, hunched posture, pinched in sides, piloerection, and wet and dry urine staining) were noted in all animals at 800 mg/kg; however, no evidence of bone marrow toxicity (decreased % PCE) was observed at the 24 or 48 hour sampling times at up to 800 mg/kg. No significant increase in micronucleated polychromatic erythrocytes (MPCEs) was observed in any dose at either 24 or 48 hours post-dosing. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirement (OPPTS 870.5395; OECD 474) for *in vivo* cytogenetic mutagenicity data. Although, the dosing formulation was not analyzed for the amount of test substance, this is not considered to be a major deficiency that would have altered the results of the study, since the test substance was tested at a toxic dose level and the testing laboratory adheres to GLP regulations, and has a QA

unit.

Contaminant SYN 519312

46203317 Callander, R. (2003) SYN 519312: Bacterial Mutation Assay in S. typhimurium and E. coli: Final Report. Project Number: YV6422. Unpublished study prepared by Central Toxicology Lab (Syngenta). 30 p.

Executive Summary - In two independent reverse gene mutation assays in bacteria (MRID 46203317), *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strains WP2 *uvr*A (pKM101) and WP2 (pKM101) were exposed to SYN 519312 (an impurity of Pinoxaden tech.; Pinoxaden; 96% a.i., Batch # BPS 1177/1) in dimethylsulfoxide (DMSO) at concentrations of 100, 200, 500, 1000, 2500, or 5000 µg/plate in the presence and absence of mammalian metabolic activation (+/-S9). The standard plate incorporation method was performed in Trial 1 (+/-S9) and Trial 2 (-S9), while a pre-incubation step was added in Trial 2 (+S9). Standard strain-specific mutagens served as positive controls.

SYN 519312 was tested up to the limit dose (5000 µg/plate). Cytotoxicity (as indicated by reduction in number of revertants) was observed in Trial 1 at 5000 µg/plate (+S9) in strains TA98, TA100, TA1537, and WP2 (pKM101), and at ≥2500 µg/plate (+S9) in strain TA1535, and in Trial 2 at 5000 µg/plate (-S9) in strains TA100 and WP2 (pKM101), and at ≥2500 µg/plate (+S9) in strain WP2 (pKM101). Precipitation of the test material was also observed at the upper 1-3 concentrations in the presence and absence of S9 in both trials. No marked increases in the number of revertants were observed at any concentration in any strain in either trial. The positive controls induced marked increases in revertant colonies compared to controls in both trials. **There was no evidence of induced mutant colonies over background.**

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirements (OPPTS 870.5100; OECD 471) for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

Appendix 3. Metabolism Considerations

A-3.0 Introduction

Pinoxaden is a new post-emergence herbicide for control of grass weeds in wheat (including durum) and barley. The proposed use of pinoxaden is one application per crop season at a rate of 0.036 - 0.062 lb a.i./A at with a PHI of 60 days and REI of 48 hours. The proposed PBI for wheat and barley is 0 day and for other crops is 30 days; however, HED has requested label amendment such that to replace "other crops" with "leafy and root crops" and also to add 120-day PBI for other cereal grains and other crops. A 30-day pre-grazing interval is also included on the label.

A-3.1 Description of Issues and Team Proposal

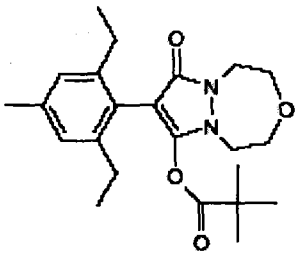
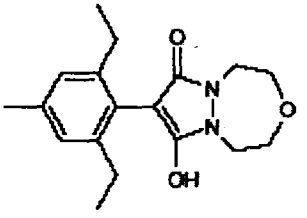
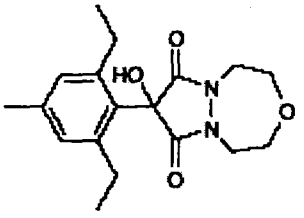
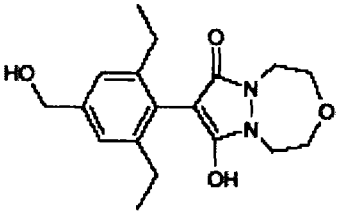
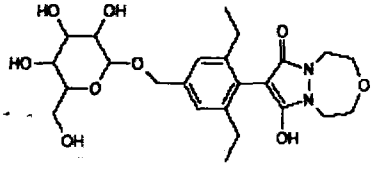
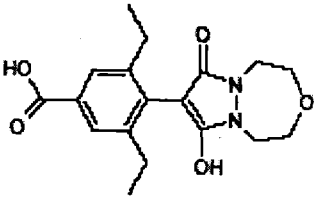
The registrant has not proposed tolerances for meat, milk, poultry and egg (MMPE) commodities since feeding studies resulted in residues less than limit of quantitation (LOQ). However, HED determined that tolerances are needed on MMPE since the feeding studies were not conducted at ≥10X and that the livestock metabolism studies indicated that residues are concentrated in some livestock tissues (liver and kidney).

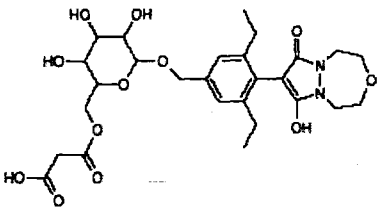
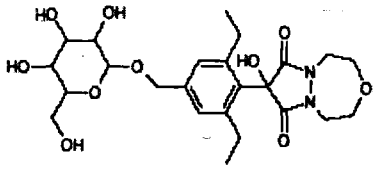
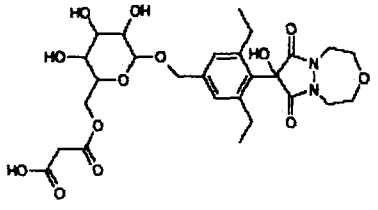
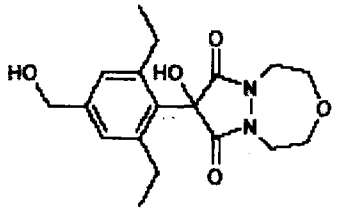
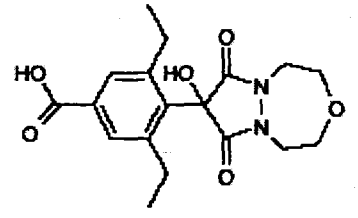
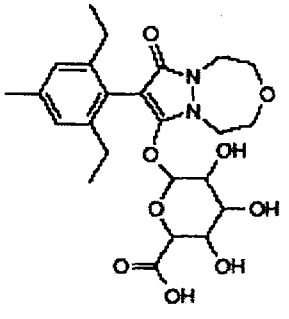
The following Table summarizes the residues of concern for risk assessment and tolerance expression.

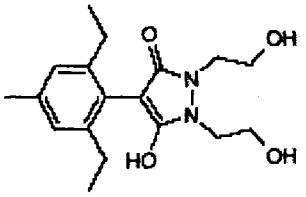
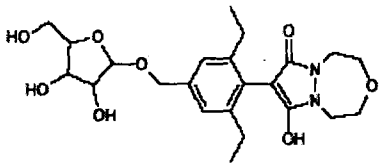
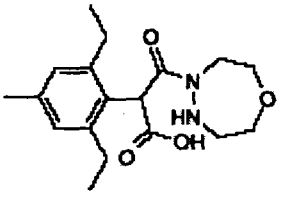
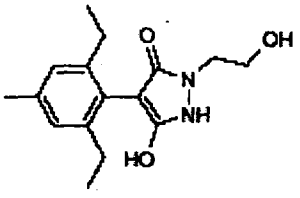
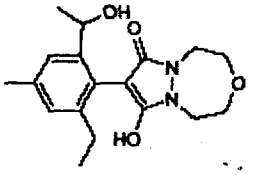
Table A-3.1.1: Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

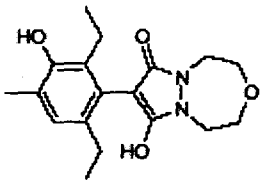
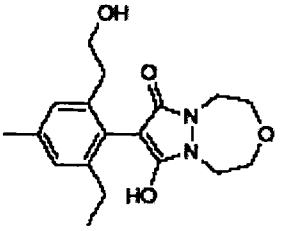
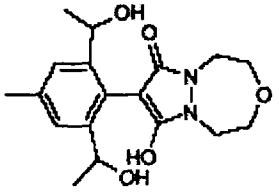
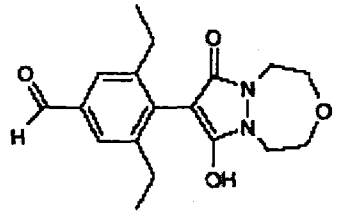
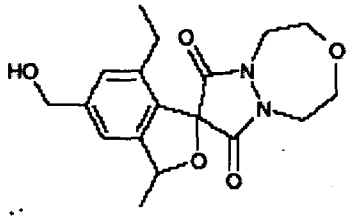
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Pinoxaden, M2, M4 (free & conjugated), M6	Pinoxaden, M2, M4 (free & conjugated), M6
	Rotational Crop	Pinoxaden, M2, M3 (free & conjugate), M10, M11	No Tolerance Required
Livestock	Ruminant	Pinoxaden, M2, M4 (free & conjugated)	Pinoxaden, M2, M4 (free & conjugated)
	Poultry	Pinoxaden, M2, M4 (free & conjugated), M6	Pinoxaden, M2, M4 (free & conjugated), M6
Drinking Water		Pinoxaden, M2, and M3	Not Applicable

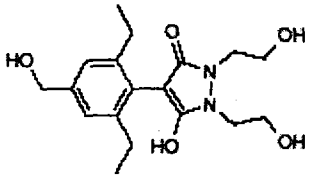
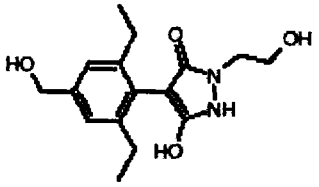
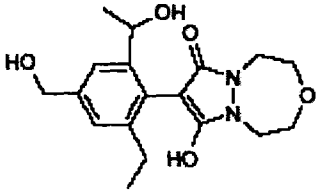
Table A-3.1.2 Structure of Parent and Metabolites from Plant and Animal Metabolism Studies.

Name	Structure	Matrix
M1 (NOA 407855) (Pinoxaden)		Wheat, Goat, Hen
M2 (NOA 407854)		Wheat, Goat, Hen, Water
M3 (NOA 447204)		Wheat, Rotational Crop, goat, Hen, Water
M4 (SYN 505164)		Wheat, Goat, Hen
M5		Wheat
M6 (SYN 502836)		Wheat, Goat, Hen

Name	Structure	Matrix
M7		Wheat
M8		Wheat, Rotational Crop
M9		Wheat
M10 (SYN 505887)		Wheat, Rotational Crop, Goat
M11 (SYN 504574)		Wheat, Rotation Crop
M12		Goat

Name	Structure	Matrix
M13		Goat
M14		Wheat
M19		Goat (feces)
M20		Goat (feces)
M22		Goat (feces)

Name	Structure	Matrix
M23		Goat (feces)
M24		Goat (feces)
M26		Goat (feces)
M31		Wheat, Hen
M32		Wheat

Name	Structure	Matrix
M33		Hen
M34		Hen
M35		Hen

A-3.2 Nature of the Residue Studies in Plants

Wheat: In order to adequately delineate the fate and disposition of ^{14}C-pinoxaden (8-(2,6-diethyl-p-tolyl)-1,2,4,5-tetrahydro-7-oxo-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-9-yl 2,2-dimethyl-propionate; also referred to as Pinoxaden or M1) in wheat, four wheat metabolism studies were performed using either spring wheat or winter wheat with pinoxaden radiolabelled either in the pyrazol, phenyl or oxadiazepine rings and treated at different timings of application (fall, early spring & late spring) and at various growth stages (BBCH 13, BBCH 21, BBCH 37-39 & BBCH 49). Furthermore, wheat crop parts were sampled over a wide range of pre-harvest intervals (PHIs) from immature forage and ears to mature grain, husk and straw.

Pinoxaden was applied as a foliar spray at a rate of either 68.5 g a.i./ha (or 0.0611 lb a.i./A; to winter wheat as an autumn application at the three leaves unfolded growth stage) including the safener but no adjuvant; or 64 or 318 g a.i./ha (or 0.057 or 0.283 lb a.i./A; to winter wheat as a spring application at the first awns visible growth stage) including the safener and an adjuvant; or 58.1 - 60.0 g a.i./ha (or 0.0518 or 0.0535 lb a.i./A; to spring wheat as an early season application at the initial tillering growth stage) including the safener and an adjuvant; or 62.0 - 66.0 g a.i./ha (or 0.0553 or 0.0588 lb a.i./A; to spring wheat as a regular spring application at the flag leaf just visible to flag leaf fully unrolled growth stage) including the safener and an adjuvant.

Radioactivity was detected in all plant parts, and as would be expected, radioactive residues were

highest in immature forage and declined rapidly. The unchanged parent molecule was detected only up to 14 DAT thus demonstrating rapid metabolization of pinoxaden. The metabolic profile of pinoxaden in wheat was similar across the three radiolabels thus indicating that there was minimal cleavage of the bonds between the rings. Throughout the four wheat metabolism studies, no substantive variation in the metabolic degradation of pinoxaden was observed. Spring wheat and winter wheat demonstrated similar metabolic profiles. The timing of application and the growth stage of the wheat plants at application did not have a significant impact on the qualitative nature of the resulting metabolic pattern, but revealed some quantitative differences. The difference could be explained by the time interval that the degradation was allowed to proceed. The longer the PHI and the more mature was the wheat plant at application, the more extensive was the metabolism.

Table A-3.2.1: Summary of Distribution of the Parent and the Metabolites in Wheat Forage when Dosed with ^{14}C-labelled Pinoxaden Following Different Treatment Regimes

Radiolabel Position (Study No.)	Pyrazol (99PSA55)		Phenyl (00PSA58)		Phenyl (01JS35)		Oxadiazepine (01JS35)		Phenyl (01MK16)		Oxadiazepine (01MK16)		Phenyl (00PSA58)		Oxadiazepine (01MK16)	
Growth Stage at Application (Application Rate)	BBCH 13 (68.5 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 21 (60 g a.i./ha)		BBCH 21 (58.1 g a.i./ha)		BBCH 37-39 (62 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)	
PHI	0 day		0 day (3 hours)		0 day (1 hour)		0 day (1 hour)		0 day (1 hour)		0 day (1 hour)		7 days		7 days	
Metabolite Fraction	Whole tops TRR = 6.731 ppm		Whole tops TRR = 1.909 ppm		Whole tops TRR = 4.420 ppm		Whole tops TRR = 2.910 ppm		Whole tops TRR = 3.447 ppm		Whole tops TRR = 3.885 ppm		Whole tops TRR =1.950 ppm		Whole tops TRR = 1.948 pp	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 80% Acetonitrile	107.6	Not given	105.3	Not given	97.3	Not given	96.1	Not given	95.4	Not given	99.3	Not given	96.0	Not given	101.5	No give
I_1	--	--	--	--	--	--	--	--	--	--	--	--	1.1	0.021	0.5	0.01
I_2 (M7)	--	--	--	--	--	--	--	--	--	--	--	--	3.6	0.070	--	--
I_{2a}	--	--	--	--	--	--	--	--	--	--	--	--	0.8	0.016	--	--
I_3 (M5)	--	--	0.5	0.009	--	--	--	--	--	--	--	--	29.5	0.575	24.5	0.47
I_4 (M9)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{4a} (M14)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2.2	0.04
I_5	--	--	--	--	--	--	--	--	--	--	--	--	0.9	0.017	--	--
I_6	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_7 (M6)	--	--	0.3	0.005	--	--	0.1	0.003	--	--	--	--	7.5	0.147	6.6	0.12
I_8	--	--	0.3	0.007	--	--	--	--	--	--	--	--	2.4	0.046	--	--
I_{8a}	--	--	--	--	--	--	--	--	0.5	0.017	0.6	0.023	--	--	--	--
I_9 (M4)	--	--	64.2	1.225	1.4	0.062	1.0	0.028	9.6	0.331	8.6	0.334	43.4	0.847	52.2	1.01
I_{9a} (M31)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{10}	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{11} (M8)	--	--	--	--	--	--	--	--	--	--	--	--	0.9	0.017	2.2	0.04
I_{12}	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{13}	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{14} (M11)	--	--	0.3	0.006	--	--	--	--	--	--	--	--	--	--	--	--
I_{15} (M2)	66.3	4.465	22.8	0.435	61.9	2.734	60.9	1.773	71.9	2.478	79.0	3.069	1.8	0.035	1.8	0.03
I_{15a} (M10)	--	--	--	--	--	--	--	--	--	--	--	--	0.6	0.011	--	--

Radiolabel Position (Study No.)	Pyrazol (99PSA55)		Phenyl (00PSA58)		Phenyl (01JS35)		Oxadiazepine (01JS35)		Phenyl (01MK16)		Oxadiazepine (01MK16)		Phenyl (00PSA58)		Oxadiazepine (01MK16)	
Growth Stage at Application (Application Rate)	BBCH 13 (68.5 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 21 (60 g a.i./ha)		BBCH 21 (58.1 g a.i./ha)		BBCH 37-39 (62 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)	
PHI	0 day		0 day (3 hours)		0 day (1 hour)		0 day (1 hour)		0 day (1 hour)		0 day (1 hour)		7 days		7 days	
Metabolite Fraction	Whole tops TRR = 6.731 ppm		Whole tops TRR = 1.909 ppm		Whole tops TRR = 4.420 ppm		Whole tops TRR = 2.910 ppm		Whole tops TRR = 3.447 ppm		Whole tops TRR = 3.885 ppm		Whole tops TRR =1.950 ppm		Whole tops TRR = 1.948 pp	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
I_{15b}	--	--	0.8	0.016	--	--	--	--	1.8	0.062	2.7	0.105	--	--	--	--
I_{15c} (M32)	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{16} (M1; pinoxaden)	36.2	2.435	9.8	0.188	30.3	1.339	27.0	0.786	7.3	0.252	5.4	0.210	1.0	0.019	1.7	0.03
I_{17} (M3)	1.9	0.128	1.1	0.022	1.3	0.057	4.7	0.137	1.0	0.034	1.2	0.047	1.3	0.026	3.7	0.07
I_{17a}	--	--	2.6	0.050	--	--	--	--	--	--	--	--	--	--	--	--
I_{18}	--	--	0.4	0.008	--	--	0.2	0.006	--	--	--	--	--	--	--	--
I_{18a}					0.1	0.005	0.2	0.006	--	--	--	--	--	--	--	--
I_{19}	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Unresolved	3.2	0.215	2.1	0.041	2.3	0.103	2.1	0.062	3.2	0.110	1.8	0.070	1.3	0.025	6.2	0.12
Non-extractable	1.0	0.067	2.2	0.042	0.6	0.027	0.7	0.020	1.4	0.047	0.8	0.030	4.4	0.086	4.3	0.08
Total extractable	107.6	Not given	105.3	Not given	97.3	Not given	96.1	Not given	95.4	Not given	99.3	Not given	96.0	Not given	101.5	No give
Total identified	104.4	7.028	99.0	1.890	94.9	4.192	93.7	2.727	89.8	3.095	94.2	3.660	89.6	1.747	94.9	1.84
Total characterized	0.0	0.0	4.1	0.081	0.1	0.005	0.4	0.012	2.3	0.079	3.3	0.128	5.2	0.100	0.5	0.01
Total bound	1.0	0.067	2.2	0.042	0.6	0.027	0.7	0.020	1.4	0.047	0.8	0.030	4.4	0.086	4.3	0.08
Accountability (extractable + bound)	108.6 %		107.5 %		97.9 %		96.8 %		96.8 %		100.1 %		100.4 %		105.8 %	

1- I13a, and I17a are other notations used for M3.
2- I1, I9, I3 and M5 are conjugated forms of M4.
3- I7 is a conjugated form of M6.

Table A-3.2.2: Summary of Distribution of the Parent and the Metabolites in Wheat Forage when Dosed with ^{14}C-labelled Pinoxaden Following Different Treatment Regimes.

Radiolabel Position (Study No.)	Pyrazol (99PSA55)		Phenyl (00PSA58)		Phenyl (01JS35)		Oxadiazepine (01JS35)		Phenyl (01MK16)		Oxadiazepine (01MK16)		Phenyl (01JS35)		Oxadiazepine (01JS35)	
Growth Stage at Application (Application Rate)	BBCH 13 (68.5 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 21 (60 g a.i./ha)		BBCH 21 (58.1 g a.i./ha)		BBCH 37-39 (62 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 21 (60 g a.i./ha)		BBCH 21 (58.1 g a.i./ha	
PHI	14 days		14 days		14 days		14 days		14 days		14 days		28 days		28 days	
Metabolite Fraction	Whole tops TRR = 0.304 ppm		Whole tops TRR = 1.434 ppm		Whole tops TRR =0.834 ppm		Whole tops TRR =0.635 ppm		Whole tops TRR =1.021 ppm		Whole tops TRR = 1.051ppm		Whole tops TRR = 0.290 ppm		Whole tops TRR = 0.155 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 80% Acetonitrile	94.4	Not given	99.6	Not given	91.8	Not given	98.2	Not given	95.3*	Not given	93.0*	Not given	96.9	Not given	98.9	No give
I_1	2.8	0.0085	0.6	0.009	0.6	0.005	0.7	0.004	2.3	0.023	1.9	0.020	1.2	0.003	2.5	0.00
I_2 (M7)	4.6	0.0140	1.0	0.014	3.0	0.025	1.5	0.009	2.8	0.029	4.4	0.046	3.6	0.011	3.8	0.00
I_{2a}	--	--	0.3	0.004	0.2	0.001	0.2	0.001	--	--	--	--	0.3	0.001	0.3	<0.00
I_3 (M5)	16.3	0.0496	29.1	0.418	48.9	0.408	35.8	0.228	38.3	0.391	36.3	0.382	50.6	0.147	57.2	0.08
I_4 (M9)	3.2	0.0098	0.5	0.008	1.4	0.012	2.5	0.016	0.3	0.003	1.9	0.020	3.4	0.010	3.0	0.00
I_{4a} (M14)	--	--	0.6	0.009	--	--	--	--	2.5	0.026	0.2	0.002	0.5	0.001	--	--
I_5	1.2	0.0036	2.0	0.029	1.5	0.012	2.7	0.017	1.1	0.011	0.7	0.007	1.9	0.005	1.8	0.00
I_6	1.2	0.0038	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_7 (M6)	3.4	0.0105	9.8	0.141	7.8	0.065	7.4	0.047	8.2	0.084	7.0	0.074	5.6	0.016	5.0	0.00
I_{7a}	--	--	0.2	0.003	0.5	0.004	0.5	0.003	--	--	--	--	0.5	0.002	0.6	0.00
I_{7b}	--	--	0.3	0.004	--	--	--	--	--	--	--	--	0.2	0.001	0.3	<0.00
I_{7c}	--	--	--	--	--	--	--	--	--	--	--	--	0.9	0.003	--	--
I_8	1.2	0.0037	1.9	0.027	1.0	0.008	1.2	0.007	1.2	0.012	0.6	0.006	0.7	0.002	0.8	0.00
I_9 (M4)	25.6	0.0779	39.2	0.562	13.7	0.114	22.8	0.145	30.5	0.311	31.0	0.326	6.7	0.020	5.5	0.00
I_{10}	0.4	0.0011	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{11} (M8)	1.5	0.0045	1.2	0.018	1.6	0.014	3.5	0.022	1.4	0.014	1.7	0.018	2.2	0.006	2.7	0.00
I_{11a}	--	--	--	--	--	--	--	--	--	--	--	--	--	--	0.3	<0.00
I_{13}	0.5	0.0016	0.3	0.004	--	--	--	--	--	--	--	--	--	--	--	--
I_{14} (M11)	0.9	0.0027	0.2	0.003	0.1	0.001	0.2	0.001	--	--	--	--	0.2	<0.001	0.2	<0.00

Radiolabel Position (Study No.)	Pyrazol (99PSA55)		Phenyl (00PSA58)		Phenyl (01JS35)		Oxadiazepine (01JS35)		Phenyl (01MK16)		Oxadiazepine (01MK16)		Phenyl (01JS35)		Oxadiazepine (01JS35)	
Growth Stage at Application (Application Rate)	BBCH 13 (68.5 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 21 (60 g a.i./ha)		BBCH 21 (58.1 g a.i./ha)		BBCH 37-39 (62 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 21 (60 g a.i./ha)		BBCH 21 (58.1 g a.i./ha	
PHI	14 days		14 days		14 days		14 days		14 days		14 days		28 days		28 days	
Metabolite Fraction	Whole tops TRR = 0.304 ppm		Whole tops TRR = 1.434 ppm		Whole tops TRR =0.834 ppm		Whole tops TRR =0.635 ppm		Whole tops TRR =1.021 ppm		Whole tops TRR = 1.051ppm		Whole tops TRR = 0.290 ppm		Whole tops TRR = 0.155 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
I_{14a}	--	--	--	--	--	--	--	--	2.4	0.025	0.6	0.006	--	--	--	--
I_{15} (M2)	5.4	0.0165	1.4	0.020	--	--	--	--	0.8	0.008	0.8	0.008	0.3	0.001	--	--
I_{15a} (M10)	--	--	0.6	0.009	0.2	0.002	0.5	0.003	--	--	--	--	0.3	0.001	--	--
I_{15d}	--	--	--	--	--	--	--	--	--	--	--	--	0.3	0.001	--	--
I_{16} (M1; pinoxaden)	4.0	0.0123	0.4	0.006	--	--	--	--	0.4	0.004	0.7	0.007	--	--	--	--
I_{17} (M3)	5.7	0.0173	1.2	0.017	0.9	0.007	1.7	0.011	1.7	0.017	0.8	0.008	5.1	0.015	4.1	0.00
I_{18}	1.0	0.0032	0.2	0.003	--	--	--	--	--	--	--	--	--	--	--	--
I_{19}	3.2	0.0099	0.7	0.010	--	--	--	--	--	--	--	--	--	--	--	--
Unresolved	12.0	0.0366	7.7	0.111	10.4	0.087	17.1	0.109	1.3	0.013	4.7	0.049	12.3	0.036	11.1	0.01
Non-extractable	11.1	0.0337	6.0	0.086	5.7	0.048	4.8	0.030	5.9	0.061	5.3	0.055	8.1	0.023	7.3	0.01
Total extractable	94.4	Not given	99.6	Not given	91.8	Not given	98.2	Not given	95.3	Not given	93.0	Not given	96.9	Not given	98.9	No give
Total identified	70.6	0.2151	85.2	1.225	77.6	0.648	75.9	0.482	86.9	0.887	84.8	0.891	78.5	0.228	81.5	0.12
Total characterized	11.5	0.0354	6.5	0.093	3.8	0.030	5.3	0.032	7.0	0.071	3.8	0.039	6.0	0.018	6.6	0.00
Total bound	11.1	0.0337	6.0	0.086	5.7	0.048	4.8	0.030	5.9	0.061	5.3	0.055	8.1	0.023	7.3	0.01
Accountability (extractable + bound)	105.5 %		105.6 %		97.5 %		103.0 %		101.2 %		98.3 %		105.0 %		106.2 %	

Value = predominant metabolites

* In Study No. 01MK16, there was two extraction steps for all samples (except 0-DAT and 7-DAT forage samples): extraction with 80% acetonitrile + microwave extraction with 80% 1-propanol [phenyl: 86.6 + 8.7 = 95.3 and oxadiazepine: 85.7 + 7.3 = 93.0]

Table A-3.2.3: Summary of Distribution of the Parent and the Metabolites in Wheat Forage, Tops & Ears when Dosed with ^{14}C-labelled Pinoxaden Following Different Treatment Regimes.

Radiolabel Position (Study No.)	Pyrazol (99PSA55)		Pyrazol (99PSA55)		Phenyl (00PSA58)		Oxadiazepine (01MK16)		Phenyl (00PSA58)		Oxadiazepine (01MK16)		Phenyl (00PSA58)	
Growth Stage at Application (Application Rate)	BBCH 13 (68.5 g a.i./ha)		BBCH 13 (68.5 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 49 (318 g a.i./ha)	
PHI	42 days		209 days		28 days		28 days		28 days		28 days		28 days	
Metabolite Fraction	Whole tops TRR = 0.109 ppm		Whole tops TRR = 0.011 ppm		Tops TRR = 2.396 ppm		Tops TRR = 1.211 ppm		Ears TRR = 0.743 ppm		Ears TRR = 0.285ppm		Ears TRR = 2.837ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 80% Acetonitrile	93.8	Not given	81.7	Not given	89.3	Not given	97.3*	Not given	95.9	Not given	96.2*	Not given	81.4	Not given
I_1	5.4	0.0059	1.9	0.0002	3.4	0.081	5.0	0.061	4.8	0.035	3.3	0.009	2.3	0.065
I_2 (M7)	9.8	0.0107	--	--	3.9	0.094	5.0	0.061	--	--	--	--	0.4	0.010
I_{2a}	--	--	--	--	0.6	0.014	--	--	0.6	0.005	--	--	--	--
I_3 (M5)	30.2	0.0330	--	--	56.3	1.349	64.4	0.780	19.2	0.143	24.1	0.069	21.1	0.600
I_4 (M9)	15.1	0.0165	7.6	0.0008	0.5	0.012	2.4	0.029	0.4	0.003	0.2	0.001	--	--
I_{4a} (M14)	--	--	--	--	--	--	0.8	0.010	1.3	0.009	0.8	0.002	1.8	0.051
I_5	1.1	0.0012	--	--	2.0	0.049	1.4	0.017	4.4	0.033	2.1	0.006	1.3	0.036
I_6	1.3	0.0014	1.4	0.0001	--	--	--	--	--	--	--	--	--	--
I_7 (M6)	4.5	0.0049	--	--	8.4	0.201	7.4	0.090	6.4	0.048	10.5	0.030	4.5	0.128
I_{7a}	--	--	--	--	0.4	0.009	--	--	--	--	--	--	--	--
I_{7b}	--	--	--	--	0.5	0.011	--	--	1.2	0.009	--	--	1.0	0.029
I_8	1.1	0.0012	--	--	1.4	0.035	--	--	4.3	0.032	--	--	2.6	0.075
I_{8a}	--	--	--	--	--	--	--	--	--	--	--	--	3.8	0.109
I_9 (M4)	9.3	0.0101	1.4	0.0002	7.3	0.176	5.6	0.068	42.7	0.317	47.8	0.136	26.7	0.759
I_{10}	1.1	0.0012	2.1	0.0002	--	--	--	--	--	--	--	--	--	--
I_{11} (M8)	3.3	0.0036	10.8	0.0012	1.1	0.027	2.4	0.029	1.0	0.007	--	--	1.2	0.035
I_{12}	0.8	0.0008	1.8	0.0002	--	--	--	--	--	--	--	--	--	--
I_{13}	0.4	0.0005	3.5	0.0004	0.1	0.003	--	--	--	--	--	--	--	--
I_{14} (M11)	0.5	0.0005	2.7	0.0003	--	--	--	--	--	--	--	--	--	--
I_{14a}	--	--	--	--	--	--	0.6	0.007	--	--	1.0	0.003	--	--

Radiolabel Position (Study No.)	Pyrazol (99PSA55)		Pyrazol (99PSA55)		Phenyl (00PSA58)		Oxadiazepine (01MK16)		Phenyl (00PSA58)		Oxadiazepine (01MK16)		Phenyl (00PSA58)	
Growth Stage at Application (Application Rate)	BBCH 13 (68.5 g a.i./ha)		BBCH 13 (68.5 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 49 (64 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 49 (318 g a.i./ha)	
PHI	42 days		209 days		28 days		28 days		28 days		28 days		28 days	
Metabolite Fraction	Whole tops TRR = 0.109 ppm		Whole tops TRR = 0.011 ppm		Tops TRR = 2.396 ppm		Tops TRR = 1.211 ppm		Ears TRR = 0.743 ppm		Ears TRR = 0.285ppm		Ears TRR = 2.837ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
I_{15} (M2)	1.4	0.0015	--	--	--	--	--	-	--	--	--	--	--	--
I_{15a} (M10)	--	--	8.9	0.0010	0.4	0.010	--	--	1.3	0.010	--	--	0.8	0.023
I_{15b}	--	--	--	--	--	--	0.6	0.007	--	--	--	--	--	--
I_{15c} (M32)	--	--	2.9	0.0003	--	--	--	--	--	--	--	--	--	--
I_{15d}	--	--	--	--	--	--	--	--	--	--	0.5	0.001	--	--
I_{16} (M1; pinoxaden)	--	--	--	--	--	--	--	--	--	--	--	--	--	--
I_{17} (M3)	3.0	0.0033	19.2	0.0021	0.2	0.005	0.7	0.008	--	--	2.0	0.006	0.4	0.012
I_{18}	--	--	2.7	0.0003	--	--	--	--	--	--	--	--	--	--
Unresolved	5.5	0.0060	14.9	0.0016	2.7	0.064	1.2	0.015	8.3	0.061	3.8	0.011	13.4	0.380
Non-extractable	12.8	0.0140	22.5	0.0025	7.1	0.170	5.2	0.063	8.8	0.065	8.6	0.025	15.0	0.426
Total extractable	93.8	--	81.7	--	89.3	--	97.3	--	95.9	--	96.2	--	81.4	--
Total identified	77.1	0.0841	53.5	0.0059	78.1	1.874	88.7	1.075	72.3	0.537	85.4	0.244	56.9	1.618
Total characterized	11.2	0.0122	13.4	0.0014	8.4	0.202	7.6	0.092	15.3	0.114	6.9	0.019	11.0	0.314
Total bound	12.8	0.0140	22.5	0.0025	7.1	0.170	5.2	0.063	8.8	0.065	8.6	0.025	15.0	0.426
Accountability (extractable + bound)	106.6 %		104.2 %		96.4 %		102.5 %		104.7 %		104.8 %		96.4 %	

Value = predominant metabolites

* In Study No. 01MK16, there was two extraction steps for all samples (except 0-DAT and 7-DAT forage samples): extraction with 80% acetonitrile + microwave extraction with 80% 1-propanol [tops: 92.2 + 5.1 = 97.3 and ears: 86.6 + 9.6 = 96.2]

Table A.3.2.4: Summary of Distribution of the Parent and the Metabolites in Mature Wheat Grain when Dosed with ^{14}C-labelled Pinoxaden Following Different Treatment Regimes.

Radiolabel Position (Study No.)	Phenyl (00PSA58)		Phenyl (00PSA58)		Pyrazol (99PSA55)		Phenyl (01MK16)		Oxadiazepine (01MK16)		Pyrazol (99PSA55)	
Growth Stage at Application (Application Rate)	BBCH 49 (64 g a.i./ha)		BBCH 49 (318 g a.i./ha)		BBCH 41 (Stem injection)		BBCH 37-39 (62 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 13 (68.5 g a.i./ha)	
PHI	55 days		55 days		56 days		67 days		67 days		264 days	
Metabolite Fraction	Grain TRR = 0.246 ppm		Grain TRR = 0.845 ppm		Grain TRR = 1.520 ppm		Grain TRR = 0.142 ppm		Grain TRR = 0.165 ppm		Grain TRR = 0.004 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 80% Acetonitrile	59.8	Not given	76.5	Not given	72.9	Not given	78.1*	Not given	79.1*	Not given	Not analyzed	
I_1	6.2	0.015	11.8	0.100	26.8	0.407	25.8	0.037	34.5	0.057		
I_2 (M7)	4.3	0.011	10.5	0.089	21.8	0.331	3.6	0.005	6.7	0.011		
I_3 (M5)	5.1	0.013	8.8	0.074	6.6	0.100	15.7	0.022	13.3	0.022		
I_5	1.2	0.003	--	--	--	--	--	--	--	--		
I_7 (M6)	9.6	0.024	13.2	0.111	12.3	0.187	12.0	0.017	13.6	0.022		
I_9 (M4)	19.7	0.048	18.2	0.154	1.7	0.026	9.4	0.013	7.7	0.013		
I_{11} (M8)	--	--	1.4	0.012	--	--	--	--	--	--		
I_{14a}	--	--	--	--	--	--	1.9	0.003	1.1	0.002		
I_{15a} (M10)	0.7	0.002	0.7	0.006	--	--	--	--	--	--		
I_{16} (M1; pinoxaden)	--	--	--	--	--	--	--	--	--	--		
Unresolved	13.0	0.032	12.0	0.101	3.7	0.057	9.7	0.014	2.1	0.003		
Non-extractable	45.9	0.113	19.4	0.164	37.5	0.570	21.8	0.031	18.7	0.031		
Total extractable	59.8	Not given	76.5	Not given	72.9	Not given	78.1	Not given	79.1	Not given	Not analyzed	
Total identified	39.4	0.098	52.8	0.446	42.4	0.644	40.7	0.057	41.3	0.068		
Total characterized	7.4	0.018	11.8	0.100	26.8	0.407	27.7	0.040	35.6	0.059		
Total bound	45.9	0.113	19.4	0.164	37.5	0.570	21.8	0.031	18.7	0.031		

Radiolabel Position (Study No.)	Phenyl (00PSA58)		Phenyl (00PSA58)		Pyrazol (99PSA55)		Phenyl (01MK16)		Oxadiazepine (01MK16)		Pyrazol (99PSA55)	
Growth Stage at Application (Application Rate)	BBCH 49 (64 g a.i./ha)		BBCH 49 (318 g a.i./ha)		BBCH 41 (Stem injection)		BBCH 37-39 (62 g a.i./ha)		BBCH 37-39 (66 g a.i./ha)		BBCH 13 (68.5 g a.i./ha)	
PHI	55 days		55 days		56 days		67 days		67 days		264 days	
Metabolite Fraction	Grain TRR = 0.246 ppm		Grain TRR = 0.845 ppm		Grain TRR = 1.520 ppm		Grain TRR = 0.142 ppm		Grain TRR = 0.165 ppm		Grain TRR = 0.004 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Accountability (extractable + bound)	105.7 %		95.9 %		110.4 %		99.9 %		97.8 %			

Value = predominant metabolites

* In Study No. 01MK16, there was two extraction steps for all samples (except 0-DAT and 7-DAT forage samples): extraction with 80% acetonitrile + microwave extraction with 80% 1-propanol [phenyl: 27.5 + 50.6 = 78.1 and oxadiazepine: 48.1 + 31.0 = 79.1]

A-3.3 Nature of the Residue in Livestock

Ruminant Metabolism Study: Two livestock metabolism studies were performed to elucidate the fate and distribution of pinoxaden and its metabolites in lactating goats. The first study (Study No. 046AM04, MRID No. 46203129) was carried out with the parent molecule (pinoxaden; Pinoxaden) radiolabelled in the phenyl ring. The second study (Study No. 751-02, MRID No. 46203134) was carried out with the metabolite M4 (SYN 505164), radiolabelled in the pyrazolo[1,2-*d*] [1,4,5] oxadiazepine ring. In the wheat metabolism studies, M4 was identified as a predominant metabolite in all wheat matrices (forage, ears, grain, straw and husks). However, M4 was not found to be a unique plant metabolite as it was also observed in animal matrices (goat, hen and rat).

In Study No. 046AM04, two lactating goats were administered 120.6 ppm in their diet of [phenyl-1-^{14}C] pinoxaden (also known as Pinoxaden or M1) for four consecutive days. The majority of the AD was eliminated over the course of the study (0 to 78 hours), with 82.62% AD in excreta (feces, urine, gastrointestinal tract and rumen). Only minor fractions of the total administered dose were transferred to milk (0.009% AD) and edible tissues (0.260% AD). The highest concentrations of ^{14}C-residues were detected in kidney (2.953 ppm) and liver (1.160 ppm). The predominant metabolite detected in all the goat matrices was M2, which is the hydrolysis product of the parent molecule pinoxaden. Multiple minor metabolites (M3, M4, M6, M22, M12, M13, M20, M19, M23, M24, M26, M27 and M28), each representing less than 10% of the TRRs, were detected in feces, as well as in some tissues and milk. Unchanged pinoxaden was not detected in any of the matrices studied, indicating its rapid and complete metabolism in the lactating goat.

In Study No. 751-02, two lactating goats received four consecutive daily administrations of 10 ppm in their diet of [7-^{14}C] M4 (also known as SYN 505164). At the time of sacrifice, the majority of the administered dose (AD) had been eliminated, with 92.89% AD in excreta (feces, urine, gastrointestinal tract and rumen). Residues in milk, muscle, fat and blood were below the LOQ (0.002 ppm in

milk and 0.011 ppm in tissues). Only minor fractions of the total administered dose were transferred to the remaining tissues (< 0.1 %AD). The highest concentrations of ^{14}C-residues in goat tissues were detected in liver and kidney (0.025 ppm and 0.044 ppm, respectively). The major metabolite, identified in all tissues containing detectable residues, was unchanged M4. The only other metabolite identified was M10 (SYN 505887) which is the hydroxylation product of M4. M10 represented only a minor fraction of the TRRs in liver and kidney and represented less than 10% of excreted TRRs in feces.

Overall, it can be concluded that pinoxaden is rapidly metabolized in all lactating goat matrices. Transfer of radioactive residues to edible tissues and milk is minimal. In goats administered the predominant plant metabolite M4, transfer of total radioactive residues to milk and edible tissues was also very low. The highest concentrations of total radioactive residues in both studies were in the liver and kidney, which is to be expected considering the rapid metabolism and excretion of pinoxaden and its metabolites. Taken together, these results indicate that residues of pinoxaden and a major plant metabolite M4 (and by inference all metabolites sharing a similar structure), have a very low transfer into the edible tissues and milk of lactating goats.

[Phenyl-^{14}C] pinoxaden was rapidly and completely metabolized in all goat matrices. The parent metabolite was thus not detected in milk, feces, urine or any of the tissues analyzed. The predominant metabolite identified in all goat matrices was M2, which is formed by the hydrolysis of the ester moiety on the parent molecule. In the [7-^{14}C] M4 metabolism study, the predominant metabolite identified in all goat matrices was unchanged M4. Hydroxylation of M4 to M10 did occur in all matrices characterized, but this represented only a minor fraction (< 10%) of the TRRs. Of note, the metabolite M10 was not detected in any of the matrices of goats administered [phenyl-^{14}C] pinoxaden.

Table A-3.3.1: Summary of Distribution of the Parent and the Metabolites in Goat Matrices when Dosed with [Phenyl-1-^{14}C] Pinoxaden at 120.6 ppm in feed.

Metabolite Fraction	Milk		Muscle		Fat		Liver		Kidney		Feces	Urine
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	%TRR
Extractable with ACN and ACN:H_2O (8:2, v:v)												
Total Residues	98.4	n.p.	95.7	n.p.	92.8	n.p.	97	n.p.	99.2	n.p.	98.6	N/A
C-18 Solid Phase Extraction (SPE) Clean-up												
Eluate 1	0.21	n.p.	0.24	n.p.	89	n.p.	N/A	-	N/A	-	N/A	N/A
Eluate 2	98	n.p.	95.5	n.p.	3.96	n.p.						
Eluate 3	0.23	n.p.	N/A	-	N/A	-						
Chromatography (HPLC)												
Pinoxaden (M1, NOA 407855)	-	-	-	-	-	-	-	-	-	-	-	-
M2 (NOA 407854)	87.8	0	89.8	0.1	78.6	0	85.9	1	90.4	2.67	90	94.9
M3 (NOA 447204)	0.4	0	-	-	-	-	-	-	2.3	0.1	1.1	-
M4	1.7	0	0.7	0	1.1	0	1.6	0	0.5	0	2.5	0.5
M6 + M22	-	-	-	-	-	-	-	-	-	-	0.9	-
M12	6.2	0	4.4	0	8.5	0	6.9	0.1	4.2	0.12	-	3.9
M13 + M20[7]	-	-	-	-	-	-	-	-	0.3	0	0.9	-
M19 + M23	-	-	-	-	-	-	-	-	-	-	0.6	-
M24 + M26 + M28	-	-	-	-	-	-	-	-	-	-	0.7	-
M27	-	-	-	-	-	-	-	-	-	-	0.4	-
Total identified	96	0	94.9	0.1	88.2	0	94.4	1.1	97.7	2.89	97.2	99.3
Unidentified	2	0	0.6	0	0.7	0	2.6	0	1.5	0	1.4	0.8
Unresolved	0.4	0	0.2	0	3.9	0	-	-	-	-	-	-
Total extractable	98.4	n.p.	95.7	n.p.	92.8	n.p.	97	n.p.	99.2	n.p.	98.6	N/A
Unextractable (PES)[8]	1.6	0	4.3	0	7.2	0	3	0	0.8	0	1.4	N/A
Accountability[9]	100%		100%		100%		100%		100%		100%	N/A

N/A - not applicable
n.p. - not provided
"-" - not detected
[1] Elution with H_2O
[2] Elution with H_2O:MeOH (5:5, v:v), followed by MeOH
[3] Elution with MeOH
[4] Elution with H_2O, H_2O:MeOH (70:30, v:v) and MeOH
[5] Elution with H_2O and H_2O:MeOH (50:50, v:v)
[6] Elution with ACN and MeOH
[7] only M13 in kidney
[8] Residues remaining after exhaustive extractions.
[9] Accountability = (Total extractable + Total unextractable)/(TRRs from combustion analysis; see TABLE C.2.1) * 100.

Table A-3.3.2: Summary of Distribution of the Parent and the Metabolites in Goat Matrices when Dosed with [7-^{14}C-] SYN 505164 at 10 ppm in feed[1].

Metabolite Fraction	Urine[2] Goat #1012		Urine[2] Goat #1013		Feces		Kidney		Liver	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Acetonitrile (ACN):Water (8:2, v:v) Extraction										
Extractable Residues	N/A		N/A		103.43	13.748	91.6	0.04	87.9	0.022
C18 SPE clean-up										
ACN:H_2O eluate	N/A		N/A		N/A		89.3	0.039	93.1	0.023
HPLC applied	100	1.438	100	0.789	103.43	13.748	89.3	0.039	93.1	0.023
SYN 505164	96.6	1.389	97.7	0.771	90.1	11.975	72.6	0.032	54.1	0.014
SYN 505887	-	-	-	-	3.5	0.467	-	-	-	-
Unidentified / Unknown	3.4	0.049	2.3	0.018	9.8	1.306	16.7	0.01	39	0.01
2d-TLC applied	N/A		N/A		N/A		72.6	0.032	54.1	0.014
SYN 505164	N/A		N/A		N/A		55	0.024	40.8	0.01
SYN 505887	N/A		N/A		N/A		9.1	0	8.1	0
Unidentified/Unknown	N/A		N/A		N/A		8.4	0	5.3	0
Total Identified	96.6	1.389	97.7	0.771	93.6	n.p.	64.1	n.p.	48.9	n.p.
Unidentified	3.4	0.049	2.3	0.018	9.8	1.306	25.15	n.p.	44.35	n.p.
Total Extractable	N/A	-	N/A	-	103.43	13.748	91.6	0.04	87.9	0.022
Unextractable (PES)[3]	N/A	-	N/A	-	0.26	0.034	1.5	<0.0015	6.5	0
Accountability[4]	100.0%		100.0%		103.7%		94.3%		96.0%	

N/A - not applicable
n.p. - not provided
"-" - not detected
[1] Milk and Fat were not extracted as the TRRs in these tissues were < LOQ (< 0.002 ppm in milk and < 0.011 ppm in tissues).
[2] 48-72 hour fraction
[3]Residues remaining after exhaustive extractions.
[4] Accountability = (Total extractable + Total unextractable)/(TRRs from combustion analysis)* 100.
[5]Unidentified residues in kidney and liver show in chromatograms as multiple peaks with low concentrations (in kidney, <5% of the TRRs each peak and in liver, the highest peak at ~13.5% of the TRRs (0.003 ppm)).

Poultry Metabolism Study: A group of five laying hens received four consecutive daily administrations of 12.5 mg [phenyl-1-^{14}C] pinoxaden (NOA 407855, M1), equivalent to 96.7 ppm in their diet. The majority of the administered dose (70.89%) had been excreted by the time of sacrifice. Only minor fractions of the total administered dose were transferred to eggs (0.007%) and edible tissues (0.158%). The highest concentration of ^{14}C-residues in tissues were detected in kidney (1.782 ppm) and liver (0.617 ppm). The predominant metabolites detected were M2 (NOA 407854), M4 (SYN 505164) and M6 (SYN 502836). M2 is the hydrolysis product of the parent pinoxaden, while M4 is formed by the hydroxylation at the 4-methyl group of the phenyl moiety of M2. M6 is formed by the oxidation of M4 (via the intermediate reaction product M31). Several minor metabolites, corresponding to less than10% of the TRRs (M3 (NOA 447204), M31, M33, M34 and M35) were detected in excreta, eggs and some tissues. Unchanged parent pinoxaden was not detected in any of the hen matrices studied.

At the time of sacrifice, 70.89% of the administered dose (AD) had been excreted. An additional 10.05% AD was recovered in the gizzard. Egg and tissue residues accounted for only 0.007%

AD and 0.1587% AD, respectively. The highest concentration of residues (expressed as pinoxaden equivalents) were detected in liver and kidney (1.782 ppm and 0.617 ppm, respectively).

The predominant reaction step in the proposed metabolic pathway for the metabolism of pinoxaden in laying hen is the hydrolysis of the ester moiety of the parent molecule to yield the metabolite M2. Hydroxylation of M2, at the 4-methyl group on the phenyl moiety leads to the formation of M4, which is further oxidized via the intermediate reaction product M31 to yield M6. The remaining identified metabolites (M3, M33, M34 and M35) constitute only minor fractions of the TRRs (<10%).

Table A-3.3.3: Summary of Distribution of the Parent and the Metabolites in Hen Matrices when Dosed with [Phenyl-1-^{14}C] Pinoxaden at a rate of 96.7 ppm in their diet.

Metabolite Fraction	Excreta	Egg White		Egg Yolk		Lean Meat		Fat and Skin		Liver	
	%TRR	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Extraction											
Fraction 1	94.41	92.53	n.p.	60.13	n.p.	90.21	n.p.	85.53	n.p.	96.84	n.p.
Fraction 2	3.22	2.62	n.p.	7.12	n.p.	2.82	n.p.	7.02	n.p.	N/A	n.p.
Exhaustive Extraction of Solids											
n-hexane	N/A	N/A	-	0.3	n.p.	N/A	-	N/A	-	N/A	-
MeOH : H_2O : HCOOH (50 : 50 : 0.1)				1.2	n.p.						
1 N HCl				11.7	n.p.						
Liquid - Liquid Partition											
n-hexane phase	N/A	N/A	-	2.3	n.p.	N/A	-	0.3	n.p.	4	n.p.
H_2O phase				57.8	n.p.			85.2	n.p.	92.8	n.p.
RP18 Solid Phase Extraction											
Eluate 1	N/A	N/A	-	0.05	n.p.	0.05	n.p.	N/A	-	9.67	n.p.
Eluate 2				57.86	n.p.	90.26	n.p.			78.36	n.p.
Chromatography (HPLC)											
Pinoxaden (parent, M1)	-	-	-	-	-	-	-	-	-	-	-
M2 (NOA 407854)	18.5	45.5	0.0059	1.7	0.0005	17	0.0102	8.6	0.0099	6.7	0.0411
M3 (NOA 447204)	0.2	-	-	-	-	-	-	-	-	-	-

M4 (SYN 505164)	43.2	27.3	0.0035	23.7	0.0073	44.3	0.0266	30.2	0.035	18	0.111
M6 (SYN 502836)	13.5	-	-	13	0.004	13.9	0.0083	22.4	0.026	45.2	0.2791
M31	1.8	-	-	-	-	-	-	1.3	0.0015	0.8	0.0048
M33	4.3	7	0.0009	3.7	0.0011	7.2	0.0043	8.6	0.0099	4.1	0.0255
M34	3.1	1.1	0.0001	3.5	0.0011	3.8	0.0023	3.2	0.0037	1.5	0.009
M35	1.5	1.5	0.0002	1.7	0.0005	-	-	2.7	0.0031	0.5	0.0033
Unidentified	8.2	10.1	0.0013	10.4	0.0032	4	0.0024	8.4	0.0097	3.2	0.0197
Total identified	86.2	82.4	0.0107	47.4	0.0147	86.2	0.0517	76.8	0.0891	76.8	0.4738
Total characterized	8.2	10.1	0.0013	10.4	0.0032	4	0.0024	8.4	0.0097	3.2	0.0197
Total extractable	97.6	95.1	n.p.	80.4	n.p.	93	n.p.	92.5	n.p.	96.8	n.p.
Unextractable (PES)[8]	2.4	4.9	0.0006	19.6	n.p.	6.9	0.0041	7.5	0.0087	3.2	0.0197
Accountability[9]	100%	100%		100%		99.9%		100%		99.9%	

[1]Extracted with ACN, ACN : H_2O (8 : 2) and MeOH : H_2O (8 : 2)
[2]Extracted with MeOH : H_2O (8 : 2)
[3]Extracted with ACN and ACN : H_2O (8 : 2)
[4]Extracted with MeOH and MeOH : H_2O (8 : 2)
[5]Eluted with 0.1% HCOOH, 0.1% HCOOH : MeOH (9 : 1), 0.1% HCOOH : MeOH (8: 2), 0.1% HCOOH : MeOH(5 : 5)
[6]Eluted with MeOH
[7]Eluted with 0.1% HCOOH
[8]Residues remaining after exhaustive extractions
[9]Accountability = (Total extractable + Total unextractable)/(TRRs from combustion analysis; see TABLE C.2.1) * 100
"-" - not detected
n.p. - not provided
N/A - not applicable

A-3.4 Confined Rotational Crop Study

In order to determine the nature and the amount of pinoxaden (8-(2,6-diethyl-p-tolyl)-1,2,4,5-tetrahydro-7-oxo-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-9-yl 2,2-dimethyl-propionate; also referred to as NOA 407855 or M1) residue uptake in rotational crops, three confined crop rotation trial studies were performed. The different studies were carried out with ^{14}C-pinoxaden radiolabelled either in the phenyl or the oxadiazepine ring. Depending on the study design, diverse rotational crops were used: mustard leaves, lettuce, radish, turnip, spring or winter wheat; and various plant-back intervals (PBIs) were tested: 15 days, 30 days, 120 days, 170 days, and 365 days. With the exception of the soil types (clay loams were used instead of the requisite sandy loam) the three confined rotational crop studies are considered scientifically acceptable. TRRs accumulated at levels greater than 0.01 ppm in mustard leaves, turnip tops, wheat forage and wheat fodder planted 15 DAT with either [phenyl-1-^{14}C]pinoxaden or [oxadiazepin-3,6-$^{14}C_1$]pinoxaden applied outdoors to bare ground (silty clay loam) at a total rate of 70 g a.i./ha (0.062 lb a.i./A). TRRs also exceeded 0.01 ppm in lettuce, radish tops, wheat forage and wheat fodder planted 29-30 days after treatment and in wheat fodder planted 120 days after treatment with either [phenyl-1-^{14}C]pinoxaden (at a total rate of 60.3 g a.i./ha or 0.054 lb a.i./A) or [oxadiazepin-3,6-$^{14}C_1$]pinoxaden (at a total rate of 65.5 g a.i./ha or 0.058 lb a.i./A).

At the 29-30 DAT PBI, none of the metabolites identified (M2, M3, M8, M9, M10, M11 & M32) were quantitated at levels greater that 0.01 ppm, except M3 in spring wheat forage (0.024 ppm; oxadiazepine radiolabel study only). Wheat forage is considered a feed item.

At the 15 DAT PBI, none of the metabolites identified [M3, M8, M10, conjugates of M10 (ME2, ME3 and ME5) & M11] were quantitated at levels greater that 0.01 ppm, except M3, M10 & M11 in spring wheat fodder (both radiolabels). Wheat fodder is considered a feed item.

Pinoxaden was not detected in any rotated crop matrices at any PBIs (from 15 to 365 days). Throughout the three confined rotational crop studies, no substantive variation in the metabolic degradation of pinoxaden was observed. Pinoxaden was hydrolyzed rapidly (disappeared by day 3) in soil yielding M2. M2 was further hydroxylated forming M3 the predominant metabolite observed in soil. M3 could thus be taken up from the soil by the rotated crops.

Metabolism of pinoxaden in rotational crops occurred mainly by hydroxylation processes. Other metabolic pathways consisted of oxidation and conjugation reaction. All the metabolites identified retained the three-ring backbone intact thus indicating there was minimal cleavage of the bonds that join the three rings.

The metabolic profile of ^{14}C-pinoxaden in wheat (primary crop) was similar to the metabolic profiles observed in the rotational studies for wheat, lettuce, mustard leaves, radish and turnip (secondary crops).

Table A-3.4.1: Summary of Distribution of the Parent and the Metabolites in Rotational Lettuce, Radish and Spring Wheat Matrices when Dosed with [Phenyl-1-^{14}C] Pinoxaden in Study No. 00PSA57.

Plant-back interval	30 DAT		30 DAT		30 DAT		30 DAT		120 DAT	
Harvest	84 DAT		84 DAT		84 DAT		141 DAT		240 DAT	
Metabolite Fraction	Lettuce Heads TRR = 0.011 ppm		Radish Tops TRR = 0.014 ppm		Spring Wheat Forage TRR = 0.024 ppm		Spring Wheat Fodder TRR = 0.035 ppm		Spring Wheat Fodder TRR = 0.038 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 80% Acetonitrile	86.1	Not given	100.9	Not given	93.6	Not given	65.7	Not given	73.3	Not given
I_1	8.1	0.0009	6.9	0.0010	8.1	0.0019	6.7	0.0023	5.4	0.0021
I_3 (M5)	--	--	--	--	2.7	0.0007	--	--	--	--
I_4 (M9)	3.2	0.0003	11.5	0.0016	20.3	0.0049	3.9	0.0014	13.7	0.0052
I_6	--	--	4.0	0.0006	--	--	3.6	0.003	2.0	0.0007
I_7 (M6)	--	--	3.9	0.0005	--	--	--	--	--	--
I_8	--	--	4.4	0.0006	--	--	--	--	--	--
I_9 (M4)	2.5	0.0003	2.5	0.0004	1.6	0.0004	1.5	0.0005	2.4	0.0009
I_{10}	--	--	--	--	3.0	0.0007	--	--	--	--
I_{11} (M8)	5.6	0.0006	20.6	0.0029	13.1	0.0031	3.3	0.0012	7.0	0.0027
I_{12}	--	--	3.5	0.0005	2.0	0.0005	--	--	--	--
I_{13}	--	--	4.1	0.0006	6.1	0.0015	2.1	0.0007	4.9	0.0019
I_{13a}	43.3	0.0048	--	--	--	--	--	--	--	--
I_{13b}	--	--	3.6	0.0005	--	--	--	--	--	--
I_{14} (M11)	--	--	1.5	0.0002	--	--	2.4	0.0008	0.3	0.0001
I_{14a}	--	--	1.6	0.0002	--	--	--	--	--	--
I_{14b}	--	--	1.3	0.0002	--	--	0.8	0.0003	--	--
I_{15} (M2)	4.8	0.0005	--	--	--	--	--	--	--	--
I_{15a} (M10)	--	--	1.5	0.0002	--	--	5.8	0.002	2.2	0.0008
I_{15c} (M32)	--	--	0.8	0.0001	--	--	4.2	0.0015	3.6	0.0014
I_{16} (M1)	--	--	--	--	--	--	--	--	--	--
I_{17} (M3)	5.3	0.0006	6.3	0.0009	17.6	0.0042	9.0	0.0032	16.1	0.0061
I_{18}	4.1	0.0004	1.8	0.0002	5.1	0.0012	4.1	0.0014	6.2	0.0023

Metabolite Fraction	Lettuce Heads TRR = 0.011 ppm		Radish Tops TRR = 0.014 ppm		Spring Wheat Forage TRR = 0.024 ppm		Spring Wheat Fodder TRR = 0.035 ppm		Spring Wheat Fodder TRR = 0.038 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Unresolved	9.3	0.001	21.0	0.0029	14.0	0.0034	18.3	0.0064	9.5	0.0036
Non-extractable	17.1	0.0019	7.7	0.0011	14.4	0.0035	40.5	0.0142	27.3	0.0104
Total identified	21.4	0.0023	48.6	0.0068	55.3	0.0133	30.1	0.0106	45.3	0.0172
Total characterized	55.5	0.0061	31.2	0.0044	24.3	0.0058	17.3	0.006	18.5	0.007
Total extractable	86.1	Not given	100.9	Not given	93.6	Not given	65.7	Not given	73.3	Not given
Total bound	17.1	0.0019	7.7	0.0011	14.4	0.0035	40.5	0.0142	27.3	0.0104
Accountability (Extractable + Bound)	103.2 %		108.6 %		108.0 %		106.2 %		100.6 %	

Value = predominant metabolite

Table A-3.4.2: Distribution of the Parent and the Metabolites in Rotational Lettuce, Radish and Spring Wheat Matrices when Dosed with [Oxadiazepin-3,6-^{14}C] Pinoxaden in Study No. 01PSA59.

Plant-back interval	29 DAT		29 DAT		29 DAT		29 DAT		120 DAT	
Harvest	70 DAT		70 DAT		70 DAT		139 DAT		249 DAT	
Metabolite Fraction	Lettuce Heads TRR = 0.014 ppm		Radish Tops TRR = 0.022 ppm		Spring Wheat Forage TRR = 0.048 ppm		Spring Wheat Fodder TRR = 0.077 ppm		Spring Wheat Fodder TRR = 0.032 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 80% Acetonitrile	99.1	Not given	97.7	Not given	91.8	Not given	63.8	Not given	76.5	Not given
I_1	4.4	0.0006	5.9	0.0013	6.3	0.003	9.9	0.0076	7.3	0.0023
I_4 (M9)	2.5	0.0003	8.8	0.0019	8.0	0.0038	5.0	0.0038	15.6	0.005
I_6	--	--	2.3	0.0005	0.6	0.0003	1.8	0.0014	1.3	0.0004
I_7 (M6)	--	--	2.9	0.0006	--	--	--	--	--	--
I_8	--	--	2.3	0.0005	--	--	--	--	--	--
I_9 (M4)	1.2	0.0002	2.2	0.0005	1.2	0.0006	1.4	0.0011	0.4	0.0001
I_{9a} (M31)	--	--	--	--	--	--	2.1	0.0017	--	--
I_{10}	--	--	--	--	0.9	0.0004	--	--	--	--
I_{11} (M8)	3.2	0.0005	25.6	0.0056	3.9	0.0019	5.2	0.004	7.0	0.0022

Metabolite Fraction	Lettuce Heads TRR = 0.014 ppm		Radish Tops TRR = 0.022 ppm		Spring Wheat Forage TRR = 0.048 ppm		Spring Wheat Fodder TRR = 0.077 ppm		Spring Wheat Fodder TRR = 0.032 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
I_{12}	--	--	5.0	0.0011	1.4	0.0007	--	--	--	--
I_{13}	--	--			2.9	0.0014	3.4	0.0026	3.5	0.0011
I_{13a}	69.1	0.0097	--	--	--	--	--	--	--	--
I_{13b}	--	--	2.5	0.0005	--	--	--	--	--	--
I_{14} (M11)	--	--	1.7	0.0004	--	--	1.8	0.0014	0.4	0.0001
I_{14a}	--	--	1.9	0.0004	--	--	--	--	--	--
I_{15} (M2)	4.1	0.0006	--	--	1.2	0.0006	--	--	--	--
I_{15a} (M10)	--	--	3.4	0.0008	--	--	3.5	0.0027	1.5	0.0005
I_{15c} (M32)	--	--	0.8	0.0002	--	--	4.0	0.0031	2.4	0.0008
I_{16} (M1)	--	--	--	--	--	--	--	--	--	--
I_{17} (M3)	3.7	0.0005	7.3	0.0016	49.3	0.0237	9.9	0.0077	23.3	0.0074
I_{18}	4.1	0.0006	2.0	0.0004	6.4	0.0031	5.0	0.0038	7.0	0.0022
Unresolved	6.8	0.001	23.2	0.0051	7.9	0.0038	10.8	0.0083	7.0	0.0022
Non-extractable	6.0	0.0008	7.0	0.0015	8.7	0.0042	37.7	0.029	27.6	0.0088
Total identified	14.7	0.0021	52.7	0.0116	63.6	0.0306	32.9	0.0255	50.6	0.0161
Total characterized	77.6	0.0109	21.9	0.0047	20.4*	0.0098*	20.1	0.0154	19.1	0.006
Total extractable	99.1	Not given	97.7	Not given	91.8	Not given	63.8	Not given	76.5	Not given
Total bound	6.0	0.0008	7.0	0.0015	8.7	0.0042	37.7	0.029	27.6	0.0088
Accountability (Extractable + Bound)	105.1 %		104.7 %		100.5 %		101.5 %		104.1 %	

Value = predominant metabolite

*Metabolite fraction I_{4a} was quantitated in spring wheat forage at 1.9% TRR (0.9 ppb).

Table A-3.4.3: Distribution of the Parent and the Metabolites in Rotational Mustard Leaves, Turnip and Spring Wheat Matrices when Dosed with [Phenyl-1-^{14}C] Pinoxaden or [Oxadiazepin-3,6-^{14}C] Pinoxaden in Study No. 174-01.

Radiolabel	Phenyl	Phenyl	Phenyl	Phenyl	Phenyl	Oxadiazepine	Oxadiazepine	Oxadiazepine
Plant-back interval	15 DAT	15 DAT	15 DAT	15 DAT	15 DAT	15 DAT	15 DAT	15 DAT

Harvest	61 DAP		89 DAP		26 DAP		50 DAP		89 DAP		26 DAP		50 DAP		89 DAP	
Metabolite Fraction	Mustard Leaves TRR = 0.013 ppm		Turnip Tops TRR = 0.010 ppm		Spring Wheat 25% Mature Forage TRR = 0.022 ppm		Spring Wheat 50% Mature Forage TRR = 0.027 ppm		Spring Wheat Fodder TRR = 0.069 ppm		Spring Wheat 25% Mature Forage TRR = 0.023 ppm		Spring Wheat 50% Mature Forage TRR = 0.021ppm		Spring Wheat Fodder TRR = 0.063 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable with 90% Acetonitrile	83.1	0.011	81.4	0.008	91.1	0.020	80.3	0.022	65.7	0.045	82.4	0.019	83.9	0.018	62.4	0.039
Aqueous Fraction	73.0	0.010	54.8	0.006	53.9	0.012	47.5	0.013	34.0	0.024	53.2	0.012	48.0	0.010	25.5	0.016
M8 (I_{11})	45.7	0.006	54.8	0.006	23.7	0.005	30.6	0.008	--	--	22.6	0.005	31.0	0.007	--	--
ME2*	10.8	0.001	--	--	5.7	0.001	6.9	0.002	--	--	6.7	0.002	5.3	0.001	--	--
ME3*	2.8	<0.001	--	--	--	--	--	--	--	--	--	--	--	--	--	--
ME5*	13.6	0.002	--	--	24.6	0.005	10.0	0.003	--	--	23.9	0.006	11.8	0.003	--	--
ME7 [I_{14} (M11)]	--	--	--	--	--	--	--	--	34.0	0.024	--	--	--	--	25.5	0.016
Organic Fraction	21.1	0.003	20.4	0.002	28.9	0.006	26.3	0.007	27.2	0.019	25.4	0.006	27.8	0.006	39.7	0.025
M3 (I_{17})	21.1	0.003	20.4	0.002	28.9	0.006	16.8	0.005	15.2	0.011	25.4	0.006	12.6	0.003	23.8	0.015
M10 (I_{15a})	--	--	--	--	--	--	9.5	0.003	12.0	0.008	--	--	10.8	0.002	15.9	0.010
Unknown	--	--	--	--	--	--	--	--	--	--	--	--	4.4	<0.001	--	--
PES	9.8	0.001	13.1	0.001	14.6	0.003	21.4	0.006	24.8	0.017	15.0	0.004	27.1	0.006	31.6	0.020
Refluxed with ACN:Water (4:1) for 24 hrs.	Not applicable								9.9	0.007	Not applicable				10.7	0.007
M6 (I_7)									2.1	0.001					2.6	0.002
M3 (I_{17})									1.7	0.001					2.3	0.001
Non-extractable									24.8	0.017					31.6	0.020
Total identified	66.8	0.009	75.2	0.008	52.6	0.011	56.9	0.016	65.0	0.045	48.0	0.011	54.4	0.012	70.1	0.044
Total characterized	27.2	0.004	--	--	30.3	0.006	16.9	0.005	--	--	30.6	0.008	21.5	0.005	--	--
Total extractable	83.1	0.011	81.4	0.008	91.1	0.020	80.3	0.022	75.6	0.052	82.4	0.019	83.9	0.018	73.1	0.046
Total bound	9.8	0.001	13.1	0.001	14.6	0.003	21.4	0.006	24.8	0.017	15.0	0.004	27.1	0.006	31.6	0.020
Accountability (Extractable + Bound)	92.9 %		94.5 %		105.7 %		101.7 %		100.4 %		97.4 %		111.0 %		104.7 %	

* Glucose-Conjugates of M10 (SYN-505887)

A-3.5 Analytical Methodology

Three analytical methodologies (REM 199.02, REM 199.03 & 117-01) were proposed for the analysis of residues of pinoxaden (NOA 407855; as metabolite M2) and the metabolites M2 (NOA 407854), M4 (SYN 505164), M6 (SYN 502836) and M10 (SYN 505887; Methods REM 199.02 & 199.03 only) in cereal matrices. All three methods possessed the same extraction procedure consisting of acid hydrolysis (1N HCl) by boiling under reflux for two hours, which is consistent with the methodology used during the wheat metabolism studies. The analysis of the resulting extract was performed by reversed-phase high-performance liquid chromatography (HPLC) using a column-switching system connected via a pneumatically and thermally assisted electrospray ionization (ESI) to a tandem mass spectrometer (HPLC-MS/MS).

All three methods have been shown to be highly specific to the target analytes through the use of tandem mass spectrometric detector (HPLC-MS/MS), therefore, neither a confirmatory method nor an interference study was required.

Furthermore, based on the extraction efficiency data provided, both analytical methods REM 199.02 (or REM 199.03) and 117-01 were successfully radio-validated in wheat matrices (grain, husk and straw) as they were capable of extracting bioincurred ^{14}C-residues at levels in accordance with the expected amounts from the wheat metabolism study. Moreover, the methods were able to extract the four metabolites of interest (M2, M4, M6 & M10) and quantitate them within the expected ranges.

Based on the submitted recovery data, on the ILV results and on the radio-validation results, analytical method 117-01 used for the quantitation of residues of M2, M4 and M6 is considered acceptable as the enforcement method in cereal matrices provided that the method is validated by ACL.

Method T001530-03 is proposed as both the data-gathering method and the enforcement method in livestock matrices for the determination of the two major pinoxaden metabolites M4 and M6.

The independent laboratory validation (ILV) of Method T001530-03 successfully demonstrated the reliability of the method for the analysis of residues of M4 and M6 in beef muscle, beef fat, milk and eggs on the first attempt. A scientifically acceptable rationale was submitted by the registrant to waive the requirement of a radio-validation study for this method. Method T001530-03 is considered acceptable as a data-gathering method for the determination of M4 and M6 in livestock matrices. The proposed

enforcement methodology for livestock is not currently adequate because it was not validated for residues of pinoxaden and M2. Based on its similarities to the plant enforcement method, HED expects that the proposed livestock method will be adequate for quantification of pinoxaden and M2. Submission of the validation data for pinoxaden and M2 may thus be a condition of registration.

A-3.6 Summary of Magnitude of Residue (MOR) Studies

A-3.6.1 Plants

Table A-3.6.1.1: Summary of Residue Data from Crop Field Trials with Pinoxaden.

Commodity (Country)	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT*	Median (STMdR)	Mean (STMR)	Std. Dev.
Combined Residues of pinoxaden, M2, M4 and M6									
Barley Hay (U.S.)	72.5	10	4	1.50	2.83	2.69	2.22	2.19	0.61
		20	4	0.17	0.23	0.22	0.19	0.20	0.02
		30	24	0.06	1.10	0.71	0.09	0.18	0.22
		40	4	0.06	0.14	0.14	0.10	0.10	0.04
Barley Straw (U.S.)	72.5	46	4	0.24	0.48	0.43	0.37	0.36	0.10
		53	4	0.26	0.65	0.46	0.41	0.43	0.16
		60	24	0.09	0.62	0.52	0.25	0.29	0.16
		67	4	0.22	0.36	0.31	0.31	0.30	0.06
Barley Grain (U.S.)	72.5	46	4	0.24	0.40	0.38	0.33	0.33	0.07
		53	4	0.32	0.64	0.48	0.47	0.48	0.13
		60	24	0.09	0.69	0.66	0.23	0.27	0.18
		67	4	0.16	0.51	0.40	0.34	0.34	0.15
Barley Hay (CDN)	70.0	15	1	0.589		0.589	--	--	--
		22	2	0.13	0.17	0.17	0.15	0.15	--
		26-36	30	0.06	0.77	0.74	0.17	0.24	0.20
		42-49	23	0.06	0.12	0.12	0.08	0.08	0.02
Barley Straw (CDN)	70.0	46	1	0.06		0.06	--	--	--
		54-70	29	0.06	0.22	0.18	0.08	0.10	0.05
		73-89	22	0.06	0.13	0.12	0.06	0.07	0.02
Barley Grain (CDN)	70.0	46	1	0.03		0.03	--	--	--
		54-70	29	0.03	0.16	0.15	0.06	0.07	0.04
		73-89	22	0.03	0.07	0.07	0.04	0.04	0.01

* HAFT = Highest Average Field Trial.

Table A-3.6.1.2: Summary of Residue Data from Crop Field Trials with Pinoxaden.

Commodity (Country)	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT*	Median (STMdR)	Mean (STMR)	Std. Dev.
Combined Residues of pinoxaden, M2, M4 and M6									
Wheat Spring Forage (U.S.)	72.5	10	6	0.96	3.58	2.84	1.16	1.66	1.03
		20	6	0.14	0.85	0.83	0.68	0.56	0.33
		30	42	0.06	0.95	0.94	0.14	0.24	0.22
		40	6	0.07	0.20	0.18	0.08	0.11	0.06
Wheat Fall Forage (U.S.)	72.5	10	2	2.53	3.46	3.00	--	3.00	--
		20	4	0.90	2.34	2.24	1.54	1.58	0.77
		30	20	0.06	3.07	2.99	1.54	1.41	0.82
		40	4	0.06	1.40	1.35	0.83	0.78	0.67
Wheat Hay (U.S.)	72.5	10	4	2.24	3.56	3.33	2.86	2.88	0.58
		20	6	0.14	2.64	2.44	1.65	1.43	1.06
		30	42	0.06	1.71	1.31	0.28	0.49	0.43
		40	6	0.09	0.51	0.47	0.15	0.24	0.18
Wheat Straw (U.S.)	72.5	46	4	0.27	0.58	0.54	0.49	0.46	0.13
		53	4	0.22	0.62	0.62	0.53	0.48	0.19
		60	42	0.09	1.49	1.23	0.34	0.43	0.32
		67	4	0.14	0.59	0.58	0.37	0.37	0.24
	217.5	60	2	0.19	0.20	0.20	--	0.20	--
	362.5	60	2	0.91	0.98	0.95	--	0.95	--
Wheat Grain (U.S.)	72.5	46	4	0.14	0.77	0.52	0.24	0.35	0.30
		53	4	0.23	0.53	0.38	0.36	0.37	0.13
		60	42	0.05	0.72	0.61	0.18	0.22	0.15
		67	4	0.45	0.65	0.55	0.49	0.52	0.09
	217.5	60	2	0.07	0.08	0.08	--	0.08	--
	362.5	60	2	0.60	0.66	0.63	--	0.63	--
Wheat Forage (CDN)	70.0	4-5	12	1.57	3.02	2.86	2.28	2.25	0.48
		6-8	31	0.66	3.75	3.21	1.50	1.53	0.60
		10-17	7	0.13	0.54	0.39	0.24	0.25	0.14
		22-25	6	0.06	0.27	0.27	0.08	0.11	0.08
		29-31	2	0.06	0.14	0.14	0.10	0.10	--
Wheat Hay (CDN)	70.0	22	1	0.87		0.87	--	--	--
		28-36	34	0.06	0.92	0.78	0.12	0.17	0.18
		37-49	20	0.06	0.14	0.14	0.09	0.09	0.02
		50	5	0.06	0.08	--	0.06	0.06	0.01
		57	1	0.06	--	--	--	--	--

Commodity (Country)	Total Application Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT*	Median (STMdR)	Mean (STMR)	Std. Dev.
		64	1	0.06	--	--	--	--	--
Wheat Straw (CDN)	70.0	58-72	37	0.06	0.19	0.19	0.07	0.08	0.03
		74-79	9	0.06	0.09	0.09	0.06	0.07	0.01
		80-88	6	0.06	0.09	0.09	0.06	0.07	0.01
		90-101	8	0.06	0.06	0.06	0.06	0.06	0
Wheat Grain (CDN)	70.0	58-72	37	0.03	0.08	0.08	0.03	0.03	0.01
		74-79	9	0.03	0.03	0.03	0.03	0.03	0
		80-88	6	0.03	0.04	0.03	0.03	0.03	0
		90-101	8	0.03	0.03	0.03	0.03	0.03	0

* HAFT = Highest Average Field Trial.

Table A-3.6.1.3: Summary of Residue Data from Barley Processing Study with Pinoxaden.

RAC	Processed Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues (M2 + M4 + M6) (ppm)	Processing Factor	Mean Processing Factor
Barley Grain	Grain	70	60	0.28		0.42X for flour 0.99X for pearled barley (Due to the discrepancy of the two values in barley bran, the concentration factors were not averaged.)
	Flour			0.12	0.43X	
	Bran			0.68	2.43X	
	Pearled Barley			0.32	1.14X	
	Grain	365	60	1.66		
	Flour			0.67	0.40X	
	Bran			1.36	0.82X	
	Pearled Barley			1.4	0.84X	

Table A-3.6.1.4: Summary of Residue Data from Wheat Processing Study with Pinoxaden.

RAC	Processed Commodity	Total Rate (g a.i./ha)	PHI (days)	Combined Residues (M2 + M4 + M6) (ppm)	Processing Factor	Mean Processing Factor
Wheat Grain	Grain	70	60	0.449		0.2X for AGF 0.2X for flour 0.7X for middling 1X for shorts 0.7X for germ (Due to the discrepancy of the two values in wheat bran, the concentration factors were not averaged.)
	AGF			0.068	0.15X	
	Bran			0.63	1.4X	
	Flour			0.089	0.2X	
	Middling			0.26	0.6X	
	Shorts			0.432	1X	
	Germ			0.273	0.6X	
	Grain	365	60	1.26		
	AGF			0.257	0.2X	
	Bran			5.81	4.6X	
	Flour			0.212	0.17X	
	Middling			0.875	0.7X	
	Shorts			1.26	1X	
	Germ			0.96	0.8X	

A-3.6.2 Livestock

Ruminants :M4 (also known as SYN 505164; 8-(2,6-diethyl-4-hydroxymethyl-phenyl)-tetrahydro-pyrazolo [1,2-*d*][1,4,5]oxadiazepine-7,9-dione) was administered once daily in a gelatin capsule via a balling gun to Holstein dairy cattle (*Bos taurus*) for 29 to 30 consecutive days. In the wheat metabolism studies, M4 was identified as a predominant plant metabolite in all wheat matrices following treatment with pinoxaden (NOA 407855).

Nine cows were administered nominal daily doses of either 1 ppm, 3 ppm or 10 ppm of M4 throughout the study period. A fourth group consisting of a control cow and a back-up cow received daily administrations of a placebo gelatin capsule. Animals were sacrificed 20 to 24 hours after the final dose.

Milk was collected twice daily and blood and tissue samples were collected at sacrifice. Liver, kidney, muscle (round and tenderloin) and fat (omental and perirenal) samples were analyzed for

residues of M4 and M6 (also known as SYN 502836), using Method T001530-03. Briefly, samples were refluxed with 1N HCl for two hours. An aliquot of the extract was subjected to two sequential solid-phase extraction (SPE) clean-up steps (SCX(2) and C_8 cartridges) and all organic solvents were removed by evaporation. Samples were diluted to an appropriate volume with 0.2% formic acid solution and an aliquot was injected directly onto a high performance liquid chromatography - tandem mass spectrometry system (HPLC-MS/MS) for analysis. Concurrent recoveries for M4 and M6 were within the acceptable guideline range of 70% to 120%. The limit of quantitation (LOQ) for each analyte was reported as 0.01 ppm in milk and 0.02 ppm in tissues.

There were no quantifiable residues (< 0.02 ppm; combined LOQs) of M4 or M6 in milk collected from animals treated at the highest dose (10 ppm), nor were any quantifiable residues (< 0.04 ppm; combined LOQs) of either metabolite detected in any of the tissues sampled. As residue levels in samples taken from animals at the highest treatment dose were all below the LOQ, no additional analysis of samples from the two lower treatment dose groups was done.

Samples were stored frozen for up to 71 days (~2.4 months) prior to analysis. A concurrent freezer storage stability study demonstrated that residues of M4 and M6 were stable in animal matrices that were stored frozen for up to 3 months. Therefore, there are no concerns with the freezer storage stability of the residues throughout the duration of the feeding study.

The dairy cattle feeding study demonstrates that residues of M4 (measured as M4 and M6) were not quantifiable in edible cow matrices when animals were administered M4 at doses up to 10 ppm in their diet.

Table A-3.6.2.1: Calculation of MTDBs of Pinoxaden to Livestock.					
Feed Item	% Diet[1]	Recommended Tolerance	% Dry Matter	% CT	Theoretical Contribution[3] (ppm)
Beef Cattle[2]					
Wheat Forage	25	3.5	25	100	3.5
MTDB	100	--	--	100	**3.5**
Dairy Cattle[2]					
Wheat Forage	60	3.5	25	100	8.4
MTDB	100	---	--	100	**8.4**
Swine					
Wheat Milled Byproduct	50	3	88	100	1.5
MTDB	100	--	--	100	**1.5**
Poultry					
Wheat Milled Byproduct	50	3	88	100	1.5
MTDB	100	–	–	100	**1.5**

1. Table 1 (OPPTS Guideline 860.1000).
2. Wheat/barley hay and straw were not included since the diet should also include protein and carbohydrates.
3. Contribution = [tolerance / % DM (cattle)] x % diet). Poultry and hog diets are not corrected for % dry matter.

Table A-3.6.2.2: Summary of Residue Data from Dairy Cattle Feeding Study with M4 (SYN 505164).							
Matrix	Feeding Level	Combined Residues of M4 and M6 (ppm)					
		n	Min.	Max.	Median (Stmdr)	Mean (STMR)	Std. Dev.
Milk	10 ppm	27	< 0.02	< 0.02	< 0.02	< 0.02	0
Liver		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Kidney		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Omental Fat		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Perirenal Fat		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Round Muscle		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Tenderloin Muscle		3	< 0.04	< 0.04	< 0.04	< 0.04	0

Poultry: M4 (also known as SYN 505164; 8-(2,6-diethyl-4-hydroxymethyl-phenyl)-tetrahydro-pyrazolo [1,2-*d*][1,4,5]oxadiazepine-7,9-dione) was administered *ad libitum* to White Leghorn

hens (*Gallus domesticus*) in treated feed for 28 consecutive days. In the wheat metabolism studies, M4 was identified as a predominant plant metabolite in all wheat matrices, following treatment with pinoxaden (NOA 407855).

Groups of 15 hens were administered feed rations containing either 0 ppm (control), 0.5 ppm, 1.5 ppm or 5.0 ppm of M4 throughout the study period. Freshly treated feed was prepared weekly and levels of feed were maintained to allow continuous feeding. Animals were sacrificed within 20 to 24 hours of the removal of treated feed.

Eggs were collected daily and tissue samples were collected at sacrifice. Samples of skin with attached fat, peritoneal fat, liver, breast muscle and thigh muscle were pooled within treatment groups and analyzed for residues of M4 and M6 (also known as SYN 502836), using Method T001530-03. Briefly, samples were refluxed with 1N HCl for two hours. An aliquot of extract was subjected to two sequential solid-phase extraction (SPE) clean-up steps (SCX(2) and C_8 cartridges) and all organic solvents were removed by evaporation. Samples were diluted to an appropriate volume with 0.2% formic acid solution and an aliquot was injected directly onto a high performance liquid chromatography - tandem mass spectrometry system (HPLC-MS/MS) for analysis. Concurrent recoveries for M4 and M6 were within the acceptable guideline range of 70% to 120%. The limit of quantitation (LOQ) for each analyte was 0.02 ppm in all matrices.

There were no quantifiable residues (< 0.04 ppm; combined LOQs) of M4 or M6 in eggs collected from animals treated at the highest dose (5.0 ppm), nor were there any quantifiable residues (< 0.04 ppm; combined LOQs) of either metabolite detected in any of the tissues sampled from the same treatment group. As residue levels in samples taken from animals at the highest treatment dose were all below the LOQ, no additional analysis of samples from the two lower treatment dose groups was done.

Samples were stored frozen for up to 99 days (~3 months) prior to analysis. A concurrent freezer storage stability study demonstrated that residues of M4 and M6 were stable in animal matrices that were stored frozen for up to 3 months. Therefore, there are no concerns with the freezer storage stability of the residues throughout the duration of the feeding study.

The laying hen feeding study demonstrated that residues of M4 and M6 were not quantifiable in edible poultry matrices when animals were administered M4 at doses up to 5 ppm in their diet.

Table A-3.6.2.3: Summary of Residue Data from Laying Hen Feeding Study with M4 (SYN 505164).

Matrix	Feeding Level	Combined Residues of M4 and M6 (ppm)					
		n	Min.	Max.	Median (STMdR)	Mean (STMR)	Std. Dev.
Milk	5 ppm	30	< 0.04	< 0.04	< 0.04	< 0.04	0
Skin + Attached Fat		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Liver		3	< 0.04	< 0.04	< 0.04	< 0.04	0

Peritoneal Fat		3	< 0.04	< 0.04	< 0.04	< 0.04	0
Breast + Thigh Muscle		3	< 0.04	< 0.04	< 0.04	< 0.04	0

Appendix 4. Dissenting Opinion of the Hazard Assessment

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **June 30, 2005**

MEMORANDUM

SUBJECT: **Pinoxaden:** New Registration - Dissenting Opinion of the Hazard Assessment

FROM: William Greear, M.P.H., D.A.B.T., Toxicologist
Registration Action Branch 1
Health Effects Division (7509C)

TO: Hope Johnson
PM
Registration Division (7505C)

DP Barcode: D310864, D311624. **Petition No. PP# 4F6817**
Chemical: Pinoxaden
PC Code: 147500

I have reviewed the latest draft of the hazard assessment concerned with the issue of carcinogenicity, sent by Mary Clock-Rust on June 30, 2005. My conclusions are as follows:

There exits an adequate carcinogenicity study in one species, the rat. There exists no adequate carcinogenicity study in a second species. HED's Carcinogenicity Assessment Review Committee (CARC) summarized the first study in mice, via gavage, in their final report:

> "The CARC concluded that the gavage mouse carcinogenicity study was inadequate, not interpretable, and not useful for risk assessment based on increased mortality at 40 mg/kg/day (40%), 300 mg/kg/day (41%) and 750 mg/kg/day (47%) in males, compared to controls (16%)."

The study was extremely flawed since mortality in male mice was not dose dependent. In addition, there was no comparable increase in mortality observed in female mice. In other words, administration of pinoxaden at the highest dose level did not produce increased female mortality when compared to controls. The non-dose dependent increase in mortality in males simply can not be explained.

HED's Carcinogenicity Assessment Review Committee (CARC) summarized the second study in mice, via diet, in their final report:

> "At the doses tested, there were no treatment-related increases in tumor incidence when compared to controls. Dosing was considered to be inadequate due to the lack of toxicity in animals in the 1500 ppm group. [The testing laboratory terminated animals in 4000 ppm group (HDT) at week 40 due to what they considered to be excessive decreases in body weight gain in males and females (31 and 33%, respectively).]", and
>
> "The subchronic study indicated that the animals could have tolerated higher doses. The CARC concluded that the dose of 1500 ppm was not high enough to assess the carcinogenicity of pinoxaden, and that the dose of 4000 ppm should have been continued."

The CARC's overall assessment of the complete toxicology data base on pinoxaden follows:

> [In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the Committee classified Pinoxaden into the category **"Data Are Inadequate for An Assessment of Human Carcinogenic Potential".**]

I am in complete agreement with the CARC's weight-of-the evidence evaluation of the potential carcinogenicity of pinoxaden.

[It must also be emphasized this is a "new chemical" of a "new chemical" class of pesticides and that a cautious approach in regulating this new chemical is warranted.]

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