5.20 PINOXADEN (293)

TOXICOLOGY

Pinoxaden is the ISO-approved common name for 2,2-dimethyl-propionic acid 8-(2,6-diethyl-4-methyl-phenyl)-9-oxo-1,2,4,5-tetrahydro-9*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-7-yl ester (IUPAC), with the CAS number 243973-20-8. It is a new herbicide that acts by inhibiting acetyl coenzyme A carboxylase.

Pinoxaden has not been evaluated previously by JMPR and was reviewed by the present Meeting at the request of CCPR.

All critical studies contained statements of compliance with GLP and were conducted in accordance with national or international test guidelines, unless otherwise specified.

Biochemical aspects

The absorption, distribution, excretion and metabolism of pinoxaden were investigated in rats following administration of either [phenyl-1-^{14}C]pinoxaden or [pyrazole-3,5-^{14}C]pinoxaden. Studies were conducted following single-dose administration in males and females and repeated-dose administration of labelled compound for 14 days in females at doses of 0.5 and 300 mg/kg bw.

Independent of dose or sex, pinoxaden was rapidly and extensively absorbed after oral administration, with maximum blood concentrations reached within 1 hour. Pinoxaden was eliminated rapidly, with 90% of the dose eliminated within 72 hours predominantly via urine (60–70% of the dose), followed by faeces (24–29%) and bile (9–12%). Bile duct–cannulated rats also excreted only about 6% or less of the dose in faeces, showing that absorption of a 0.5 mg/kg bw dose exceeded 90%.

Maximum concentrations of radiolabel in blood were reached within 1 hour after a single dose of 0.5 mg/kg bw and declined rapidly to near the limit of determination at 8 hours and 24 hours after dosing in males and females, respectively. The mean half-life was calculated to be about 1 hour for the initial elimination phase in male and female rats and was estimated to be approximately 6 hours for the terminal elimination phase. Following administration of a 300 mg/kg bw dose, concentrations of radioactivity in blood increased rapidly in both sexes, reaching the maximum concentration between 0.25 and 12 hours after dosing and thereafter declining to below the limit of quantification at 48 and 72 hours in male and female rats, respectively. No marked sex dependence of the AUC was observed. The ratio of the AUC values in blood for the high and low doses was in the range of 1100–1500, whereas the ratio between the doses was 600, suggesting that some enterohepatic recirculation occurs at the higher dose level.

Residues in tissues were low, with the highest residues in blood, liver and kidney; there was no indication of accumulation. On cessation of dosing, all tissue residues declined rapidly; more than 90% of the administered dose was recovered within 24 hours. Following this initial decline, the apparent terminal phase half-lives ranged from 1 to 3 days.

There were no qualitative or significant quantitative differences in the metabolic profiles in urine and faeces following single or multiple dosing, irrespective of sex and dose. Pinoxaden was completely metabolized, with no unchanged parent present in urine, bile or faeces. Metabolites generally represented products of hydrolysis, hydroxylation and conjugation. The major metabolite was the hydrolysis product 8-(2,6-diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxa-diazepine-7,9-dione (M2; NOA 407854), representing 77–91% of the administered dose at 300 mg/kg bw and 62–70% of the administered dose at 0.5 mg/kg bw. The only other major metabolite, 8-(2,6-diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-7-one (M4; SYN 505164), represented 7% of the administered dose at 300 mg/kg bw and 10–16% of

the administered dose at 0.5 mg/kg bw. All other metabolites identified (up to 33) were minor, being components of seven fractions, each of which represented less than 1.2% of the administered dose.

Therefore, the main metabolic pathway of pinoxaden is via hydrolysis of the ester moiety to NOA 407854, followed by glucuronide and sulfate conjugation. Hydroxylation of the 4-methyl group of the phenyl moiety transforms NOA 407854 to SYN 505164, followed by further oxidation and conjugation.

Toxicological data

In rats, the acute oral LD_{50} was greater than 5000 mg/kg bw, the acute dermal LD_{50} was greater than 2000 mg/kg bw and the acute inhalation LC_{50} was 4.63 mg/L. Pinoxaden is not irritating to the skin of rabbits, but is irritating to the eyes. Pinoxaden is not a skin sensitizer in guinea-pigs (Magnusson-Kligman), but it is in mice (local lymph node assay).

The short-term toxicity of pinoxaden was tested in rats, mice and dogs, and long-term toxicity was tested in mice and rats. Pinoxaden produced reductions in body weight gain and feed consumption at higher dose levels in all species. In rats and mice, the liver and kidney were target organs.

In a 90-day study in which pinoxaden was administered to mice via gavage at 0, 10, 100, 400, 700 or 1000 mg/kg bw per day, the NOAEL was 400 mg/kg bw per day, based on decreased body weight gain in males and decreased relative liver weight in males and females at 700 mg/kg bw per day.

In a 28-day rat study in which pinoxaden was administered via gavage at 0, 300, 600 or 1000 mg/kg bw per day, the NOAEL was 300 mg/kg bw per day, based on histopathological findings in the kidneys (tubular atrophy), increased relative liver and kidney weights, increased urine volume, increased water consumption in males, and increased urine ketones and clinical chemistry parameters (urea and creatinine) in males at 600 mg/kg bw per day.

In a 90-day rat study in which pinoxaden was given via gavage at 0, 3, 10, 30, 100 or 300 mg/kg bw per day, the NOAEL was 100 mg/kg bw per day, based on changes in clinical chemistry (increased urea and creatinine; decreased glucose in males), urine parameters (increased urine volume and ketones; decreased pH in males) and kidney microscopic findings (mineralization and neutrophil infiltration) in males treated at 300 mg/kg bw per day.

In a 90-day dietary study in rats fed pinoxaden at 0, 150, 1000, 5000 or 10 000 ppm (equal to 0, 14.9, 97.5, 466 and 900 mg/kg bw per day for males and 0, 16.0, 111, 527 and 965 mg/kg bw per day for females, respectively), the NOAEL was 1000 ppm (equal to 97.5 mg/kg bw per day), based on increased blood creatinine levels in females and decreased cholesterol levels in both sexes at 5000 ppm (equal to 466 mg/kg bw per day).

In a 90-day dog study in which pinoxaden was administered via capsule at 0, 25, 100, 250 or 500 mg/kg bw per day, the NOAEL was 100 mg/kg bw per day, based on decreased feed consumption, decreased body weight and clinical signs in both sexes at 250 mg/kg bw per day. The observations of salivation in both sexes, retching in males and clinical chemistry changes (increased alkaline phosphatase) in both sexes at 100 mg/kg bw per day were considered likely to be related to local gastrointestinal effects.

In a 1-year dog study in which pinoxaden was given via capsule at 0, 5, 25 or 125 mg/kg bw per day, the NOAEL was 125 mg/kg bw per day, the highest dose tested. Minor changes in clinical chemistry and blood cell parameters were observed up to the highest dose tested; however, these effects were considered likely to be related to local gastrointestinal effects.

The overall NOAEL was 125 mg/kg bw per day, and the overall LOAEL was 250 mg/kg bw per day.

In an 18-month study in which pinoxaden was given to mice via gavage at 0, 5, 40, 300 or 750 mg/kg bw per day, the NOAEL for systemic toxicity was 5 mg/kg bw per day, based on mortality in both sexes and reduced body weight gain in females at 40 mg/kg bw per day. There was no treatment-related increase in tumour incidence in this study, except for an equivocal incidence of lung tumours in males. The Meeting noted concerns about the conduct and interpretation of this study, including the significant number of deaths due to gavage error and the lack of clarity regarding the appropriateness of some of the statistical analyses.

Two investigative studies conducted to understand the factors contributing to the reduced survival seen in the 18-month gavage study in the mouse support the hypothesis that misplaced application of a gavage dose can result in direct access to the lungs and cause the low survival rate seen in this study.

In a second 18-month mouse study in which pinoxaden was given via the diet at 0, 150, 500, 1500 or 4000 ppm (equal to 0, 16.3, 60.7, 181 and 574 mg/kg bw per day for males and 0, 20.2, 75.7, 217 and 706 mg/kg bw per day for females, respectively), the NOAEL for systemic toxicity was 150 ppm (equal to 20.2 mg/kg bw per day), based on decreased body weight in females at 500 ppm (equal to 75.7 mg/kg bw per day). No treatment-related increases in tumour incidence were observed in this study.

In a 2-year rat study in which pinoxaden was given via gavage at 0, 1, 10, 100, 250 or 500 mg/kg bw per day, the systemic NOAEL was 10 mg/kg bw per day, based on histopathological changes in the kidneys at 100 mg/kg bw per day and associated changes in water intake and urine volume. Hepatocellular adenomas were present in the liver of 5/59 females at 500 mg/kg bw per day compared with 2/60 in controls; however, in the absence of preneoplastic lesions in any repeated-dose studies in rodents, the Meeting concluded that the increase in liver adenomas was incidental. Leiomyosarcomas of the stomach were present in 2/60 males at 250 mg/kg bw per day (males from the 500 mg/kg bw per day group were prematurely terminated) compared with 0/59 in controls. The Meeting considered the slight increase in leiomyosarcomas of the stomach in males (above the concurrent control and the historical control for the performing laboratory) to be incidental, based on the occasional occurrence of leiomyosarcomas of the stomach seen in females at a lower dose but not at higher doses in the current study, the occurrence of leiomyosarcomas in other tissues in both control and treated animals in this study with no relationship to dose and the absence of preneoplastic lesions. In addition, endometrial adenocarcinomas were noted in the uterus of females at 500 (4/59), 250 (3/60) and 100 (2/59) mg/kg bw per day, respectively, compared with 1/60 controls. The incidence of endometrial adenocarcinomas increased at the highest dose level and was above the historical control data mean. However, as no preneoplastic findings could be identified, the Meeting concluded that the increased incidence at the highest dose tested was equivocal.

The Meeting concluded that pinoxaden is not carcinogenic in mice and caused an equivocal increase in the incidence of endometrial adenocarcinomas in rats.

Pinoxaden was tested for genotoxicity in an adequate range of in vitro and in vivo assays. It gave a positive response in two in vitro cytogenetic assays, but it was negative in the in vivo mouse micronucleus and unscheduled DNA synthesis assays.

The Meeting concluded that pinoxaden is unlikely to be genotoxic in vivo.

In view of the lack of genotoxicity in vivo, the absence of carcinogenicity in mice and the equivocal effect in rats at high doses, the Meeting concluded that pinoxaden is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation reproductive toxicity study in which rats were administered pinoxaden by gavage at 0, 10, 50, 250 or 500 mg/kg bw per day, the parental NOAEL was 50 mg/kg bw per day, based on increased absolute and relative liver weights and histopathological findings in the liver (glycogen deposition) in F_0 and F_1 females at 250 mg/kg bw per day. The NOAEL for reproductive toxicity was 500 mg/kg bw per day, the highest dose tested. The NOAEL for offspring toxicity was

250 mg/kg bw per day, based on decreased F_1 pup weights at the end of the lactation period at 500 mg/kg bw per day.

In a developmental toxicity study in rats given pinoxaden by gavage at 0, 3, 30, 300 or 800 mg/kg bw per day, the NOAEL for maternal toxicity was 30 mg/kg bw per day, based on reduced body weight gain and feed consumption at 300 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 30 mg/kg bw per day, based on incomplete ossification of interparietal, metatarsal-1 and posterior distal phalanges (digit 4) bones at 300 mg/kg bw per day.

In a developmental toxicity study in rabbits administered pinoxaden by gavage at 0, 3, 10, 30 or 100 mg/kg bw per day, the NOAEL for maternal toxicity was 30 mg/kg bw per day, based on reduced body weight, body weight gain and feed consumption at 100 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 30 mg/kg bw per day, based on reduced fetal weight at 100 mg/kg bw per day. A slightly increased incidence of defects of the diaphragm (hernia in two fetuses/litters and fissure in one fetus/litter) also occurred at 100 mg/kg bw per day.

In a non-standard developmental toxicity study in rabbits, pinoxaden was given by gavage at 0 or 100 mg/kg bw per day. The purpose of this study was to clarify the potential association of genetic influence of semen donor (buck 119) with the occurrence of defects of the diaphragm by assessing the reproducibility of the developmental toxicity study in rabbits after administration of pinoxaden at 100 mg/kg bw per day during pregnancy (days 7–28) using only donor buck 119. The results showed that the dose level of 100 mg/kg bw per day resulted in maternal toxicity (reduction in feed consumption and body weight development, one case of abortion and one case of total implantation loss). At this dose level, there were two dead fetuses. At visceral fetal examination, no malformations of the diaphragm were observed in any fetuses.

In a second non-standard developmental toxicity study in rabbits, pinoxaden was given by gavage at 0 or 100 mg/kg bw per day. The purpose of this study was to investigate the potential genetic influence on the effects (diaphragm hernia/fissure) seen in the developmental toxicity study in rabbits. The study was conducted by testing whether this malformation (hernia/fissure) could be repeated in rabbits after administration of pinoxaden during pregnancy (days 7–28) using male donors of the same strain but excluding buck 119. Results showed a reduction in feed consumption and body weight gain, one case of death and two cases of abortion, and higher values of early resorption and post-implantation loss at 100 mg/kg bw per day. Visceral fetal examination revealed no malformation of the diaphragm.

In a second full guideline-compliant developmental toxicity study in rabbits given pinoxaden by gavage at 0, 3, 10, 30 or 100 mg/kg bw per day, the NOAEL for maternal toxicity was 30 mg/kg bw per day, based on decreased body weights, body weight gain and feed consumption at 100 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 30 mg/kg bw per day, based on total litter resorption at 100 mg/kg bw per day.

Defects of the diaphragm were observed in one out of four studies. All studies used the same strain of rabbits, and all but one were performed in the same laboratory. Combining the numbers of litters from all studies, the Meeting considered the observed diaphragm defects to be incidental.

The overall NOAEL for maternal toxicity was 30 mg/kg bw per day, based on decreased body weight, body weight gain and feed consumption at 100 mg/kg bw per day. The overall NOAEL for embryo and fetal toxicity was 30 mg/kg bw per day, based on total litter resorption, abortions and post-implantation loss at 100 mg/kg bw per day.

The Meeting concluded that pinoxaden is not teratogenic.

In an acute neurotoxicity study in rats given pinoxaden by gavage at 0, 100, 500 or 2000 mg/kg bw, the NOAEL was 2000 mg/kg bw, the highest dose tested.

In a 90-day rat neurotoxicity study in which pinoxaden was given by gavage at 0, 10, 100 or 500 mg/kg bw per day, the NOAEL for neurotoxicity was 500 mg/kg bw per day, the highest dose

tested. The NOAEL for systemic toxicity was 100 mg/kg bw per day, based on increased microscopic (focal tubular basophilia) findings in kidneys of males and females at 500 mg/kg bw per day.

The Meeting concluded that pinoxaden is not neurotoxic.

Toxicological data on metabolites and/or degradates

Metabolite 3 (NOA 447204)

Metabolite 3 (M3; 8-(2,6-diethyl-4-methyl-phenyl)-8-hydroxy-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione) is a rat metabolite (≤ 1.2% of the applied dose). Acute oral and short-term toxicity studies and five genotoxicity studies were performed with this metabolite.

The acute oral LD_{50} in female rats was estimated to be 1098 mg/kg bw.

In a 28-day dietary study in rats fed metabolite M3 at 0, 500, 3000, 6000 or 10 000 ppm (equal to 0, 64.9, 388, 806 and 1405 mg/kg bw per day for males and 0, 66.9, 383, 770 and 1423 mg/kg bw per day for females, respectively), the NOAEL was 3000 ppm (equal to 388 mg/kg bw per day), based on reduced body weight, changes in clinical chemistry and reduced urine volume in males at 6000 ppm (equal to 806 mg/kg bw per day).

In a 90-day dietary study in rats fed metabolite M3 at 0, 150, 1000 or 6000 ppm (equal to 0, 15, 99.2 and 601 mg/kg bw per day for males and 0, 15.2, 98.8 and 645 mg/kg bw per day for females, respectively), the NOAEL was 1000 ppm (equal to 98.8 mg/kg bw per day), based on reduced body weight in females and clinical changes in both sexes at 6000 ppm (equal to 601 mg/kg bw per day).

Metabolite M3 was tested in an adequate range of in vitro and in vivo assays. There was some evidence of clastogenicity in vitro but not in vivo. The Meeting concluded that metabolite M3 is unlikely to be genotoxic in vivo.

The Meeting concluded that metabolite M3 is of no greater toxicity than pinoxaden.

Metabolite 4 (SYN 505164)

Metabolite 4 (M4; 8-(2,6-diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo-[1,2-*d*][1,4,5]oxadiazepin-7-one) is found in rats as a major metabolite (16% of the dose in urine) and intermediate for a number of other rat metabolites. No specific toxicological data are available, but the Meeting concluded that metabolite M4 would be covered by toxicological studies on the parent.

Metabolite 6 (SYN 502836)

Metabolite 6 (M6; 3,5-diethyl-4-(9-hydroxy-7-oxo-1,2,4,5-tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-8-yl)-benzoic acid) is found in rats (< 1% of the applied dose in urine). Acute oral and short-term toxicity studies and three genotoxicity studies were performed with this metabolite.

The acute oral LD_{50} in rats was greater than 2000 mg/kg bw.

In a 28-day dietary study in rats fed metabolite M6 at 0, 300, 3000, 6000 or 12 000 ppm (equal to 0, 33.8, 334, 659 and 1310 mg/kg bw per day for males and 0, 33.6, 328, 627 and 1287 mg/kg bw per day for females, respectively), the NOAEL was 12 000 ppm (equal to 1287 mg/kg bw per day), the highest dose tested.

In a 90-day dietary study in rats fed metabolite M6 at 0, 300, 3000 or 12 000 ppm (equal to 0, 23.9, 247 and 978 mg/kg bw per day for males and 0, 26.8, 266 and 1035 mg/kg bw per day for females, respectively), the NOAEL was 12 000 ppm (equal to 978 mg/kg bw per day), the highest dose tested.

Metabolite M6 was tested in an adequate range of in vitro assays. No evidence of genotoxicity was found, and the Meeting concluded that M6 was unlikely to be genotoxic.

The Meeting concluded that metabolite M6 is of lower toxicity (at least 10-fold) than pinoxaden.

Metabolite 10 (SYN 505887)

Metabolite 10 (M10; 8-(2,6-diethyl-4-hydroxymethyl-phenyl)-8-hydroxy-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione) is found in rats (< 1% of the applied dose in urine). Acute oral toxicity and five genotoxicity studies were performed with this metabolite.

The acute oral LD_{50} in female rats was estimated to be greater than 2000 mg/kg bw.

Metabolite M10 was tested in an adequate range of in vitro and in vivo assays. There was some evidence of mutagenicity in vitro, but not in vivo. The Meeting concluded that metabolite M10 was unlikely to be genotoxic in vivo.

Based on structural considerations, the Meeting concluded that metabolite M10 is of no greater toxicity than pinoxaden.

Human data

No information was provided on the health of workers involved in the manufacture or use of pinoxaden. No information on accidental or intentional poisoning in humans is available.

The Meeting concluded that the existing database on pinoxaden was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI for pinoxaden of 0–0.1 mg/kg bw, based on a NOAEL of 10 mg/kg bw per day for histopathological changes in the kidneys and associated changes in water intake and urine volume in a 2-year rat toxicity and carcinogenicity study and using a safety factor of 100. This ADI provides a margin of about 5000 for the LOAEL for equivocal carcinogenic effects in rats.

The Meeting established an ARfD of 0.3 mg/kg bw, based on a NOAEL of 30 mg/kg bw per day for reduced maternal body weight, body weight gain and feed consumption and embryo/fetal toxicity in a developmental toxicity study in rabbits and using a safety factor of 100.

The ADI and ARfD can be applied to the metabolites M3, M4, M6 and M10, which are of no greater toxicity than pinoxaden.

Levels relevant to risk assessment of pinoxaden

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	150 ppm, equal to 20.2 mg/kg bw per day	500 ppm, equal to 75.7 mg/kg bw per day
		Carcinogenicity	4 000 ppm, equal to 574 mg/kg bw per day[b]	–
	Eighteen-month study of toxicity and carcinogenicity[c]	Toxicity	5 mg/kg bw per day	40 mg/kg bw per day
		Carcinogenicity	40 mg/kg bw per day	300 mg/kg bw per

Species	Study	Effect	NOAEL	LOAEL
				day
Rat	Twenty-four-month study of toxicity and carcinogenicity[c]	Toxicity	10 mg/kg bw per day	100 mg/kg bw per day
		Carcinogenicity	250 mg/kg bw per day	500 mg/kg bw per day[d]
	Two-generation study of reproductive toxicity[c]	Parental toxicity	50 mg/kg bw per day	250 mg/kg bw per day
		Offspring toxicity	250 mg/kg bw per day	500 mg/kg bw per day
		Reproductive toxicity	500 mg/kg bw per day[b]	–
	Developmental toxicity study[c]	Maternal toxicity	30 mg/kg bw per day	300 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	300 mg/kg bw per day
	Acute neurotoxicity study[c]	Neurotoxicity	2 000 mg/kg bw[b]	–
		Toxicity	2 000 mg/kg bw[b]	–
	Subchronic neurotoxicity study[c]	Neurotoxicity	500 mg/kg bw per day[b]	–
		Toxicity	100 mg/kg bw per day	500 mg/kg bw per day
Rabbit	Developmental toxicity studies[c,e]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
Dog	Ninety-day and 1-year toxicity studies[c,e]	Toxicity	125 mg/kg bw per day	250 mg/kg bw per day
Metabolite M3				
Rat	Thirteen-week study of toxicity[a]	Toxicity	1 000 ppm, equal to 98.8 mg/kg bw per day	6 000 ppm, equal to 601 mg/kg bw per day
Metabolite M6				
Rat	Thirteen-week study of toxicity[a]	Toxicity	12 000 ppm, equal to 978 mg/kg bw per day[b]	–

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage or capsule administration.

[d] Equivocal effect for endometrial adenocarcinomas.

[e] Two or more studies combined.

Acceptable daily intake (ADI; applies to pinoxaden and metabolites M3, M4, M6 and M10, expressed as pinoxaden)

0–0.1 mg/kg bw

Acute reference dose (ARfD; applies to pinoxaden and metabolites M3, M4, M6 and M10, expressed as pinoxaden)

0.3 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to pinoxaden

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and > 80%
Distribution	Liver, kidney and blood; some enterohepatic recirculation
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid and complete
Metabolism in mammals	Extensively metabolized via hydrolysis, hydroxylation, dealkylation, ring cleavage and ring formation reactions, followed by conjugation with glucuronide and other sugars and sulfate
Toxicologically significant compounds in animals and plants	Pinoxaden, M3, M4, M6, M10
Acute toxicity	
Rat, LD_{50}, oral	> 5 000 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	4.63 mg/L (nose-only exposure)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Irritating
Mouse, dermal sensitisation	Sensitizing (local lymph node assay)
Guinea-pig, dermal sensitization	Non-sensitizing (Magnusson-Kligman)
Short-term studies of toxicity	
Target/critical effect	Kidney and clinical chemistry
Lowest relevant oral NOAEL	97.5 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Kidney
Lowest relevant NOAEL	10 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice; equivocal increase in endometrial

	adenocarcinomas in rats[a]
Genotoxicity	
	Some evidence of clastogenicity in vitro, but no other evidence of genotoxicity[a]
Reproductive toxicity	
Target/critical effect	Parental: absolute and relative liver weight increase and histopathological liver findings (glycogen deposition) in F_0 and F_1 females (rat)
	Reproductive: no effect (rat)
	Offspring: reduced F_1 pup weight (rat)
Lowest relevant reproductive NOAEL	500 mg/kg bw per day (rat)
Lowest relevant parental NOAEL	50 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	250 mg/kg bw per day (rat)
Developmental toxicity	
Target/critical effect	Reduced maternal body weight, body weight gain, feed consumption; total resorptions, abortions and post-implantation loss
Lowest relevant maternal NOAEL	30 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	30 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested (rat)
Subchronic neurotoxicity NOAEL	500 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	No data
Studies on metabolites	
Metabolite M3	LD_{50} (rat): 1 098 mg/kg bw (females)
	28-day rat: NOAEL 388.1 mg/kg bw per day
	90-day rat: NOAEL 98.8 mg/kg bw per day
	Not genotoxic in vivo
Metabolite M6	LD_{50} (rat): > 2 000 mg/kg bw
	28-day rat: NOAEL 1 287 mg/kg bw per day
	90-day rat: NOAEL 978 mg/kg bw per day
	Not genotoxic in vitro
Metabolite M10	LD_{50} (rat): > 2 000 mg/kg bw
	Not genotoxic in vivo
Human data	
	No information provided

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI[a]	0–0.1 mg/kg bw	Long-term toxicity and carcinogenicity study (rat)	100
ARfD[a]	0.3 mg/kg bw	Developmental toxicity study (rabbit)	100

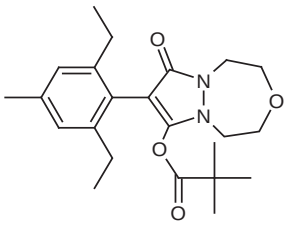
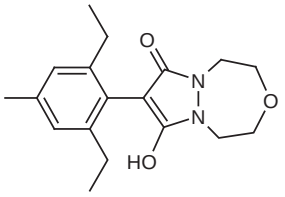
[a] Applies to pinoxaden and metabolites M3, M4, M6 and M10, expressed as pinoxaden.

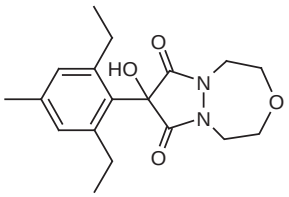
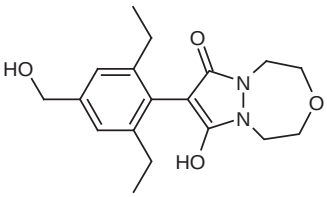
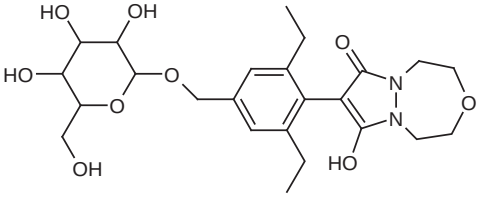
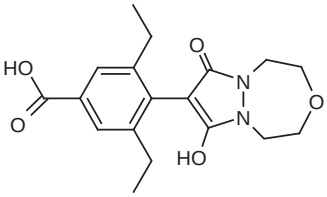
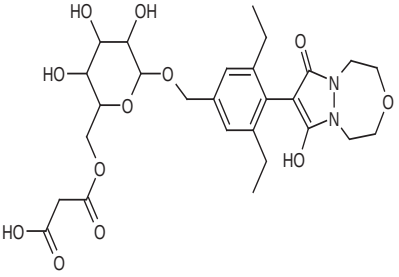
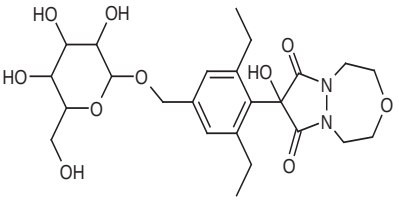
RESIDUE AND ANALYTICAL ASPECTS

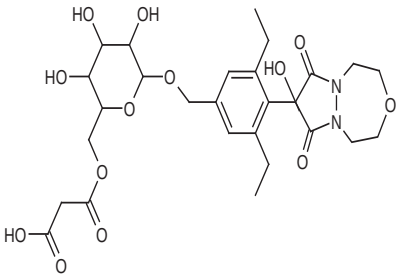
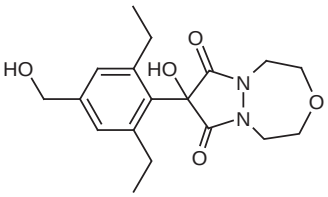
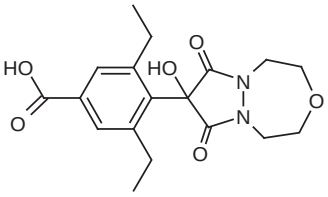
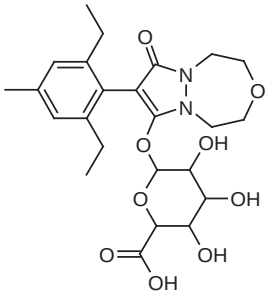
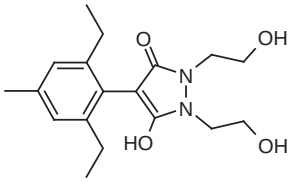
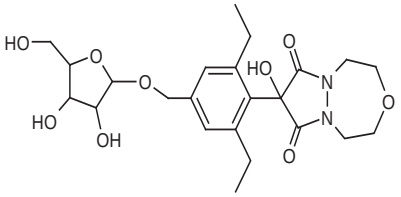
Pinoxaden is a selective post-emergence herbicide for the control of annual grass weeds in cereal crops. Pinoxaden belongs to the phenylpyrazole class of herbicides which act by inhibiting the enzyme acetyl-CoA carboxylase (ACCase). The compound was evaluated for the first time by the 2016 JMPR for both toxicology and residues.

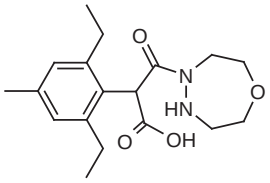
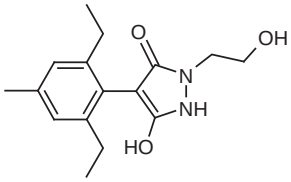
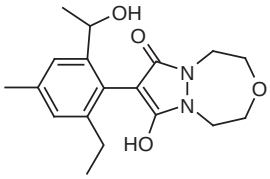
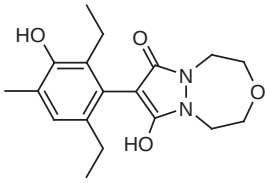
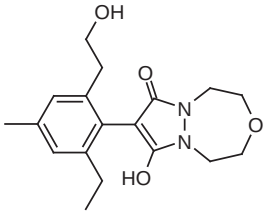
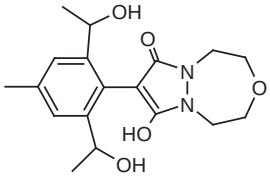
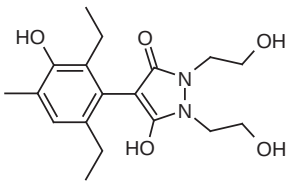
The Meeting received information on the metabolism of pinoxaden in lactating goats, laying hens, wheat and rotational crops, methods of residue analysis, freezer storage stability, GAP information, supervised residue trials and processing studies on wheat and barley as well as livestock transfer studies in both dairy cattle and poultry.

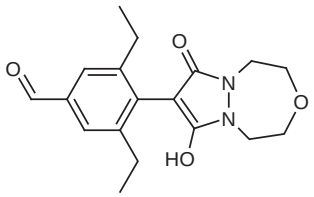
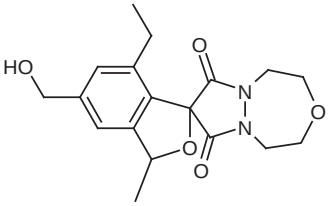
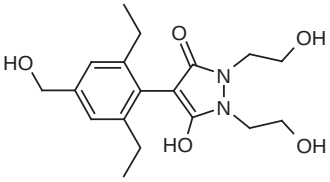
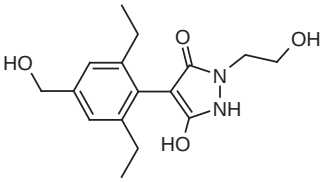
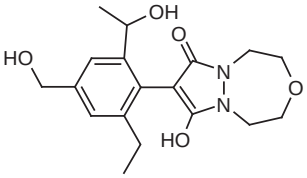
In this document, the code names, chemical structures and chemical names of the metabolites were as follows:

Compound Name	Structure	IUPAC-Name	Occurrence in
Pinoxaden NOA 407855 = M1		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	Plants and animals
NOA 407854 = M2		8-(2,6-Diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione	Winter Wheat (early intervals) Spring Wheat (early intervals) Goat Hen (excreta) Rat

Compound Name	Structure	IUPAC-Name	Occurrence in
NOA 447204 = M3		8-(2,6-Diethyl-4-methyl-phenyl)-8-hydroxy-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione	Winter Wheat Hen Rotational Wheat Rotational Lettuce
SYN 505164 = M4		8-(2,6-Diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Winter Wheat Spring Wheat Goat Hen Rat
M5 (glucose conjugate of M4)		8-[2,6-Diethyl-4-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxymethyl)-phenyl]-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Winter Wheat Spring Wheat Rat
SYN 502836 = M6		3,5-Diethyl-4-(9-hydroxy-7-oxo-1,2,4,5-tetrahydro-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-8-yl)-benzoic acid	Winter Wheat Spring Wheat Hen Goat Rat
M7 (malonyl-glucose conjugate of M4)		Malonic acid mono-{6-[3,5-diethyl-4-(9-hydroxy-7-oxo-1,2,4,5-tetrahydro-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-8-yl)-benzyloxy]-3,4,5-trihydroxy-tetrahydro-pyran-2-ylmethyl} ester	Winter Wheat Spring Wheat
M8 (glucose conjugate of M10)		8-[2,6-Diethyl-4-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxymethyl)-phenyl]-8-hydroxy-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-	Winter Wheat Spring Wheat

Compound Name	Structure	IUPAC-Name	Occurrence in
		7,9-dione	
M9 (malonyl-glucose conjugate of M10)		Malonic acid mono-{6-[3,5-diethyl-4-(8-hydroxy-7,9-dioxo-hexahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-8-yl)-benzyloxy]-3,4,5-trihydroxy-tetrahydro-pyran-2-ylmethyl} ester	Winter Wheat
SYN 505887 = M10		8-(2,6-Diethyl-4-hydroxymethyl-phenyl)-8-hydroxy-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepine-7,9-dione	Winter Wheat Spring Wheat Goat Rat
SYN 504574 = M11 = ME7		3,5-Diethyl-4-(8-hydroxy-7,9-dioxo-hexahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-8-yl)-benzoic acid	Winter Wheat Spring Wheat Rat Rotational crop forage
M12		6-[8-(2,6-diethyl-4-methyl-phenyl)-9-oxo-1,2,4,5-tetrahydro-9H-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-yloxy]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid	Goat Rat
M13		4-(2,6-diethyl-4-methyl-phenyl)-5-hydroxy-1,2-bis-(2-hydroxy-ethyl)-1,2-dihydro-pyrazol-3-one	Goat Rat
M14 (pentose conjugate of M4)		8-[4-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yloxymethyl)-2,6-diethyl-phenyl]-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-	Winter Wheat Spring Wheat Rat

Compound Name	Structure	IUPAC-Name	Occurrence in
		one	
M19		2-(2,6-diethyl-4-methyl-phenyl)-3-[1,4,5]oxadiazepan-4-yl-3-oxo-propionic acid	Goat Rat
M20		4-(2,6-diethyl-4-methyl-phenyl)-5-hydroxy-1-(2-hydroxy-ethyl)-1,2-dihydro-pyrazol-3-one	Goat Rat
M22		8-[2-ethyl-6-(1-hydroxy-ethyl)-4-methyl-phenyl]-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Goat Rat
M23		8-(2,6-diethyl-3-hydroxy-4-methyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Goat Rat
M24		8-[2-ethyl-6-(2-hydroxy-ethyl)-4-methyl-phenyl]-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Goat Rat
M26		8-[2,6-bis-(1-hydroxy-ethyl)-4-methyl-phenyl]-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Goat Rat
M27		4-(2,6-diethyl-3-hydroxy-4-methyl-phenyl)-5-hydroxy-1,2-bis-(2-hydroxy-ethyl)-1,2-dihydro-pyrazol-3-one	Goat

Compound Name	Structure	IUPAC-Name	Occurrence in
M31		3,5-Diethyl-4-(9-hydroxy-7-oxo-1,2,4,5-tetrahydro-7H-pyrazolo[1,2-d] [1,4,5]oxadiazepin-8-yl)-benzaldehyde	Winter Wheat Hen
M32		7-ethyl-5-(hydroxymethyl)-3-methyl-3H-spiro[2-benzofuran-1,8'-pyrazolo[1,2-d][1,4,5]oxadiazepine]-7',9'-dione	Winter wheat Spring Wheat Rotational Crops
M33		4-(2,6-diethyl-4-hydroxymethyl-phenyl)-5-hydroxy-1,2-bis-(2-hydroxy-ethyl)-1,2-dihydro-pyrazol-3-one	Hen
M34		4-(2,6-diethyl-4-hydroxymethyl-phenyl)-5-hydroxy-1-(2-hydroxy-ethyl)-1,2-dihydro-pyrazol-3-one	Hen Rat
M35		8-[2-ethyl-6-(1-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one	Hen Rat

Plant metabolism

The metabolism of pinoxaden, labelled in the [pyrazol-3,5-^{14}C], [phenyl-1-^{14}C] and the [oxadiazepin-3,6-^{14}C] rings, was investigated in spring and winter wheat grown under outdoor conditions.

Foliar treatment

Winter wheat (variety Galaxie) was treated as an autumn application with pinoxaden, labelled in the **pyrazole** ring and formulated as an emulsifiable concentrate formulation containing the safener cloquintocet-mexyl. The test material was applied once at growth stage BBCH 13 as a foliar spray at a rate of 68.5 g ai/ha. Samples of forage (immature plant) were harvested 0, 14, 42, and 209 days after application. Mature plants were harvested 264 days after application and separated into grain, straw and husk.

Overall total radioactive residues (TRRs) in mature grain were very low (0.004 mg eq/kg) and hence further identification was not conducted. For straw, approximately 64% of the TRRs were extracted using acetonitrile/water. Acid hydrolysis of the unextracted radioactivity, accounting for 35% of the TRR (0.013 mg/kg) released an additional 13% of the TRR. The only metabolite observed was the metabolite M10 (<3.3% of the TRR).

Stem injection

A stem injection experiment was conducted in order to generate grain and straw samples containing higher measurable residues to aid in metabolite identification. At early booting stage (BBCH 41), 50 µg of -pyrazole-labelled pinoxaden was directly injected into the stem, approximately 1–2 cm above the first node, of each spring wheat plant (variety Toronit), grown in a growth chamber. Wheat was sampled after 14, 28 and 56 days, but only the mature plants (56 DAT) were separated into grain, husk and straw and used for analysis.

The TRR in grain was considerably higher (1.5 mg eq/kg) than that following foliar application, allowing for the identification of the metabolites. Soxhlet extraction of the residue remaining following acetonitrile/water extraction released 12% of the TRR, with M4 and M6 being the only metabolites observed (concentrations not reported in the study). Further hydrolysis work on the unextracted residue (23% of the TRR) indicated that a low amount of the radioactivity (about 2% of the TRR) was incorporated into starch. When extracted with 0.05 N NaOH and hydrolysed using 1 N HCl at 100 °C for 6 hours, the metabolites M4 and M6 (both accounting for < 16% of the TRR; < 0.24 mg eq/kg) were identified.

Conversely, direct acid hydrolysis of whole grain released 100% of the TRRs and after clean-up, the majority of the radioactivity was shown to be M4 (86% of the TRR) with a small amount of M6 (8% of the TRR). This demonstrated that the majority of the radioactivity in grain consisted of conjugates of M4.

Differences in the metabolite pattern between the foliar and the stem injection experiments were noted. Moreover, in the field experiment, the presence of the metabolite M10 was likely due to uptake of the soil metabolite M3 which is subsequently hydroxylated in the plant to the metabolite M10.

Winter wheat (variety Galaxie) was treated as an autumn application with pinoxaden, labelled in the **phenyl** ring and formulated as an emulsifiable concentrate formulation. The test material was applied once at growth stage BBCH 49 as a foliar spray at rates of 64 g ai/ha (1 × rate) or 318 g ai/ha (5 × rate).

At 28 days after treatment (DAT), ears were sampled while mature plants were harvested at 55 DAT and separated into grain, straw and husks.

TRRs in the 5 × grain and straw, accounting for 0.84 mg eq/kg and 16 mg eq/kg, respectively, were 3-fold higher than those from the 1 × experiment.

Extractability of TRRs in grain was higher for the 5 × samples (76% of the TRR) in comparison with the 1 × samples (60% of the TRR). The predominant metabolites in grain were M4 (18–20% of the TRR; 0.05–0.15 mg eq/kg), its malonyl conjugate M7 (4–11% of the TRR; 0.01–0.09 mg eq/kg) and M6 (9.6–12% of the TRR; 0.02–0.11 mg eq/kg). Minor metabolites included M5, M8 and M10 (each representing ≤ 10% of the TRR; ≤ 0.01 mg eq/kg). The unextracted residue in the 1 × grain accounted for 46% of the TRR (0.11 mg eq/kg) while it accounted for 19% of the TRR (0.16 mg eq/kg) in the 5 × grain. To characterize the bound residues, grain samples from the 1 × experiment were subjected to acid hydrolysis with 1 N HCl for 6 hours at 100 °C. Metabolite M4 accounted for the majority of the released radioactivity (79% of the TRR) with M6 accounting for about 11% of the TRR, indicating that the grain unextracted residues predominantly consisted of M4 and M6 or conjugates thereof.

Approximately 78% of the TRRs in straw were extracted with an 80% acetonitrile solution. The predominant metabolites were M4 (15–37% of the TRR; 1.8-2.0 mg eq/kg) and M10 (1 × experiment only: 13% of the TRR; 0.7 mg eq/kg). Several minor metabolites were found in straw from both the 1 × and 5 × experiments including M3, M6, M7, M8, M11, M14 and M31 with M32 only found in the straw sample from the 5 × rate, none of which accounted for > 10% of the TRR). Unextracted radioactivity in the straw sample from the 1 × experiment accounted for 17% of the TRR (0.93 mg eq/kg). Acid hydrolysis of this fraction released 6.2% of the TRR and subsequent base hydrolysis released a further 8.2% of the TRR. The major metabolites released upon hydrolysis were M4 (29–60% of the TRR) and M6 (17–18% of the TRR). The unextracted residues of the straw sample from the 5 × experiment (25% of the TRRs, 3.1 mg eq/kg) were not further subjected to identification/characterisation procedures.

Spring wheat (variety Toronit) was treated with pinoxaden, labelled in the phenyl and oxadiazepine rings and formulated as an emulsifiable concentrate formulation containing the safener cloquintocet-mexyl. The test material was applied once at growth stage BBCH 37–39 as a foliar spray at a rate of 62 g ai/ha for the phenyl label and 66 g ai/ha for the oxadiazepine label. Samples of grain and straw were collected 67 DAT for both labels.

In general, TRRs were similar for both labels, especially at maturity for grain (0.14–0.16 mg eq/kg) and straw (0.91–1.3 mg eq/kg).

In grain nearly 80% of the radioactivity was extracted using acetonitrile/water followed by microwave extraction with 80% n-propanol. Hydrolysis of the cold and microwave extracts with 1N HCl released up to 92% of the TRR. In the case of the phenyl label, the released radioactivity consisted almost entirely of M4 (58% of the TRR) and M6 (6.8% of the TRR). For the oxadiazepine label, the major metabolites M4 and M6 accounted for 65% and 12% of the TRRs, respectively.

Up to 79% of the TRR was extracted from straw using acetonitrile/water (80:20, v/v). The major metabolite was M4 accounting for 34-36% of the TRR (0.33-0.44 mg eq/kg). The metabolite M6 was also found at levels up to 9% of the TRR. Several minor metabolites were identified including M3, M5, M7, M10, M11 and M32, each representing ≤ 9% of the TRR; ≤ 0.08 mg eq/kg). Unextracted radioactivity in straw accounted for 22% of the TRR (0.20 mg eq/kg) for the phenyl label and 28% of the TRR (0.36 mg eq/kg) for the oxadiazepine label. A significant amount of this residue was released by acid hydrolysis, and was attributed to metabolites M4 (0.8–1.3% of the TRR) and M6 (2.4–2.7% of the TRR).

In summary, the major metabolic pathway in wheat proceeds via ester hydrolysis of pinoxaden to M2 and subsequently to M4 followed by conjugation. Oxidation of M4 resulted in the formation of M10 which was subsequently conjugated. Lastly, further oxidation of the methyl-hydroxy function of M4 leads to the corresponding carboxylic acid M6.

The Meeting noted that all metabolites observed in wheat were also identified in the rat metabolism.

Animal metabolism

Metabolism studies were conducted in lactating goats where they were dosed orally once daily for 4 consecutive days with [**phenyl-1-^{14}C**]-pinoxaden at a dose level equivalent to 115–126 ppm feed. The major route of elimination of the radioactivity was via the urine which accounted for 45–48% of the total administered dose (AD), while feces accounted for 15–21% of the AD and milk accounted for ≤ 0.01% of the AD. The tissue burden was very low (< 1% of the AD) considering the dosing levels. The overall recovery of administered radioactivity averaged 86%.

The total radioactive residues (TRRs) were highest in kidney (1.7–4.6 mg eq/kg) followed by liver (0.9–1.4 mg eq/kg), muscle (0.06–0.1 mg eq/kg for both leg muscle and loin muscle), fat (0.01–0.04 mg eq/kg) and milk (0.01–0.02 mg eq/kg). Sequential extractions of tissues and milk with acetonitrile and acetonitrile/water released greater than 92% of the TRR.

Pinoxaden was not observed in any tissue or milk. The hydrolysis product of the parent compound, M2, was the major metabolite in all these tested matrices accounting for 79–90% of the TRR. Several minor metabolites were observed, none of which exceeded 10% of the TRR.

The metabolism of the major plant metabolite M4 was also investigated in lactating goats dosed orally once daily for 4 consecutive days with [Pyrazole-5-^{14}C]-M4 at a dose level of 9–11 ppm feed.

The major route of elimination of the radioactivity was via the feces which accounted for 58–62% of the AD, while urine accounted for 8–9% of the AD and milk accounted for ≤ 0.01% of the AD. The tissue burden was very low (< 0.1% of the AD). The overall recovery of administered radioactivity averaged 92%.

The total radioactive residues (TRRs) were highest in kidney (0.05 mg eq/kg) followed by liver (0.02–0.03 mg eq/kg). TRRs in milk were < 0.002 mg eq/kg while those in fat and muscle were each < 0.011 mg eq/kg, demonstrating very limited transfer of residues. As the radioactivity in muscle, fat and milk were low, the nature of the residues in these matrices was not further elucidated. In liver and kidney, approximately, 88–92% of the TRR was extracted with acetonitrile/water.

The major component identified in kidney and liver was unchanged M4 (41–55% of the TRR; 0.01-0.02 mg eq/kg). Minor amounts of the hydroxylated metabolite M10 were also identified (≤ 9% of the TRR; ≤ 0.004 mg eq/kg). Therefore, the predominant metabolic route was hydroxylation of M4 at the 8-position to form M10.

Leghorn laying hens were dosed orally once daily for 4 consecutive days with [**phenyl-1-^{14}C**] labelled pinoxaden at dose levels equivalent to 97 ppm feed. Approximately 85% of the AD was recovered, most of which (75% of the AD) was excreta-related. TRRs in egg white and egg yolk accounted for about 0.007% of AD (0.003% AD in egg white plus 0.004% AD in yolk). The TRR levels in egg white reached a plateau by Day 3 of dosing, however, no plateau was observed in egg yolk. The tissue burden was very low (< 0.2% of the AD) with highest concentrations found in kidney (1.8 mg eq/kg) followed by liver (0.62 mg eq/kg), skin (0.12 mg eq/kg), lean meat (0.06 mg eq/kg)and peritoneal fat (0.04 mg eq/kg). Sequential extractions of tissues and egg whites with acetonitrile, acetonitrile/water and methanol/water released greater than 92% of the TRR while for egg yolks the extractability was 67% of the TRR.

No pinoxaden was detected in any of the samples. The major metabolites in all tissues and eggs were M2 (1.7–46% of the TRR), M4 (18–44% of TRR) and M6 (13–45% of TRR; only observed in egg yolks). Four minor metabolites were also observed in these matrices, none of which exceeded 10% of the TRRs.

The Meeting concluded that, in all species investigated, the total administered radioactivity was predominantly eliminated in excreta. While the metabolic profiles differed quantitatively between the species, qualitatively there are no major differences; the routes and products of metabolism in animals were similar across the studies resulting from the hydrolysis of the parent compound to the major metabolite M2 followed by hydroxylation of the 4-methyl group of the phenyl moiety to the metabolite M4. This was followed by further oxidation of M4 to M6.

Environmental fate

The FAO Manual (FAO, 2016) explained the data requirements for studies of environmental fate. The focus should be on those aspects that are most relevant to MRL setting. For pinoxaden, supervised residue trials data were received for foliar spray on annual crops. Therefore, according to the FAO Manual, only studies on rotational crops (confined, field), aerobic degradation, hydrolysis and photolysis were evaluated.

Confined rotational crops

The Meeting received three confined rotational crop studies where pinoxaden was labelled in the **[phenyl-1-^{14}C], [oxadiazepin-3,6-^{14}C]** and both [**phenyl-1-^{14}C**] and [**oxadiazepin-3,6-^{14}C1**] rings and formulated as emulsifiable concentrate formulations. The radioalabelled material was applied once to soil at rates of 60.3–70 g ai/ha. Lettuce, radish and wheat (spring and winter) were planted 29-30, 120, 168–177 (wheat only) and 361–365 days after soil treatment. Spring wheat, mustard greens and turnip were also planted at a 15-day PBI.

The TRRs in all crop fractions planted following the longer PBIs (168-365 days) were well below 0.01 mg/kg. Hence no further work was conducted on samples from these intervals. Therefore, analysis was only conducted on fractions where residues were above 0.01 mg eq/kg. For all tested matrices, residues of the parent compound, pinoxaden, were not detectable.

Several metabolites were identified including M2, M3, M8, M9, M11 and M32, none of which exceeded 0.01 mg eq/kg, however, the metabolite M3 generally accounted for the highest proportions (9–29% of the TRR; 0.0006–0.012 mg eq/kg) in all tested commodities. Enzymatic hydrolysis of some of the extracted residues as well as acid hydrolysis of the unextracted residues revealed that 5–55% of the TRRs were attributed to free and conjugated M10 (< 0.001–0.008 mg eq/kg).

In summary, the main metabolite observed in rotational crops was M3 which was in turn hydroxylated to M10. These metabolites were all identified in the primary crop (wheat) metabolism studies, albeit at non-detectable levels in grain.

Field rotational crops

Pinoxaden, formulated as an emulsifiable concentrate formulation, was applied to the primary crop, wheat, as a single application at a rate of 69 g ai/ha, equivalent to the registered GAP. Spinach, radish, and oat crops were planted 60 and 90 days after the application (60 and 90-day plant-back intervals (PBI)).

At the 60-day PBI, no quantifiable residues (< 0.01 ppm) of the metabolite were found in any of the edible portions of the harvested commodities.

Based on this information, measurable residues of M3 are not expected in follow crops, when planted in rotation with wheat and barley treated in accordance with the registered GAP.

Soil degradation

The Meeting received soil degradation studies where **^{14}C-phenyl-, ^{14}C-pyrazole- and ^{14}C-oxadiazepine** labelled pinoxaden were each applied to soil and incubated at 20–25 °C in the dark under aerobic conditions. The soil samples were analysed after 181 days (phenyl label) and 100 days (pyrazole and oxadiazepine labels).

The volatiles were identified exclusively as carbon dioxide, demonstrating mineralization which accounted for > 45% of the applied radioactivity.

Pinoxaden was rapidly hydrolysed to M2 followed by oxidation to M3, which was further degraded. The maximum observed concentration of M2 was 88% of the AR (after 1 day), and the maximum observed concentration of M3 was 17% of the AR (between 7 and 30 days).

Under aerobic conditions pinoxaden was degraded rapidly by hydrolysis of the ester bond to M2. M2 was then degraded with a half-life of 2–16 days, forming M3 that was in turn degraded with a half-life of 7–51 days.

The Meeting also received a soil degradation study which investigated the rate of aerobic degradation of **^{14}C-pyrazole ring labelled M3** in three different soils. ^{14}C-labelled M3 was applied at a dose rate equivalent to a single field application rate of 63 g ai/ha (representing the maximum

registered seasonal application rate). The soils were incubated under aerobic conditions in the laboratory under dark conditions at 20 °C ± 2 °C for up to 120 days.

Mineralization to carbon dioxide reached comparable levels in all soils with maximum levels ranging from 13-19% of the applied dose by the end of the incubation.

The amount of unchanged M3 extracted from the soil decreased continuously throughout the study in all three soil types, with DT_{50} values between 130 to 220 days. In conclusion, the degradation of pinoxaden in soil maintained under aerobic conditions is rapid with formation of the major degradation products M2 and M3. Neither pinoxaden nor the metabolite M2 are persistent in soil ($DT_{50} \leq 16$ days), however, the metabolite M3 appears to be relatively more persistent ($DT_{50} \leq 220$ days).

Hydrolytic degradation

^{14}C-phenyl-labelled pinoxaden was incubated in diluted aqueous buffer solution at a concentration of 5 mg/L at temperatures of 15 °C (pH 7 and pH 9), 25 °C (pH 5, 7, and 9) under sterile conditions in the dark.

Pinoxaden was relatively stable to hydrolysis at pH 5 and 7 (DT_{50} of 10–23 days) but undergoes rapid hydrolysis at pH 9 (DT_{50} of ≤ 0.6 days), suggesting that hydrolysis is a significant route of degradation and occurs faster at higher pHs. The main hydrolysis degradate was M2 which was stable at all pHs and temperatures tested.

^{14}C-pyrazole labelled M3 was incubated in dilute aqueous buffer solution at a concentration of 5 mg/L under sterile conditions in the dark under the following conditions:at pH 7 at 25 °C (30 days of incubation).

Under neutral conditions (pH 7) M3 hydrolysed with a DT_{50} of 58 days at 25 °C.

Four minor metabolites resulting from the hydrolysis of the metabolite M3 were observed, however, none accounted for >10% of the AR. In summary, hydrolysis is a major degradation route of pinoxaden, with metabolites M2 and M3 being less susceptible to hydrolysis under environmental conditions.

Photolysis

During irradiation at 25 °C, pinoxaden degraded rapidly to M2, with a DT_{50} of 22 days. M2 was further photolytically degraded by the light with a DT_{50} of 8 days. In the dark, pinoxaden was also hydrolytically degraded to M2, with a comparable DT_{50} of 18 days yet M2 was not further degraded in the dark. Therefore, photolysis appears to be a major route of degradation of pinoxaden.

Methods of analysis

Methods have been reported in the scientific literature for the analysis of pinoxaden in food, including multi-residue methods. These methods do not involve a hydrolysis step, therefore, the measured residue is reported as pinoxaden, *per se*.

The wheat metabolism studies demonstrated that pinoxaden was only detected in forage samples harvested soon after application, however, as the plant matured, pinoxaden was rapidly hydrolysed to the major metabolite M2 followed by hydroxylation/oxidation and subsequent conjugation. Therefore, any residues of pinoxaden that may be present in wheat and barley commodities would be converted to M2 and all conjugates of the metabolites M4 and M10 would undergo hydrolysis. Consequently, the methods REM199.02/199.03 and 117-01, which involve extraction with 1N HCl by boiling under reflux for 2 hours, were deemed adequate to quantify residues of M2, M4 (and its conjugates), M6 and M10 (and its conjugates) in wheat and barley supervised trials and processing studies

To validate the extraction efficiency of methods REM 199.02/199.03 and 117-01, samples of grain, straw and husks from the winter wheat metabolism study were extracted by heating under reflux in 1N HCl for 2 hours or by heating under reflux in 1M HCl:acetonitrile (90:10, v:v). The overall extractabilities achieved with the analytical methods REM199.02/199.03 and 117-01 were comparable to those achieved using the procedure in the metabolism study. Therefore, these analytical methods are capable of successfully extracting residues for quantitative analysis.

A QuEChERS method was also developed for the metabolites M4 and M6 in plant commodities, but did not include a hydrolysis step. Therefore, this method was found unsuitable for measuring residues of the conjugated forms of the metabolite M4.

The Meeting also received the description and validation data for an analytical method capable of quantifying residues of the metabolites M4 and M6 in animal commodities.

All residue analytical methods rely on LC-MS/MS. Typical LOQs achieved for plant and animal commodities fall in the range of 0.01–0.02 mg/kg/analyte. Methods were successfully validated by independent laboratories, demonstrating good reproducibility.

Stability of pesticide residues in stored analytical samples

The Meeting received storage stability studies under conditions at -18 °C for pinoxaden and its relevant metabolites M2, M4, M6 and M10 for the duration of the storage of 28 months in wheat whole plant, straw, grain and processed commodities. The Meeting concluded that residues of pinoxaden and M2, M4, M6 and M10 are stable for at least 28 months in cereal commodities.

Freezer storage stability studies on animal matrices demonstrated that residues of M4 and M6 in milk, egg, chicken muscle, and beef liver, when stored frozen at -20 °C or lower, were stable for 90 days.

Definition of the residue

In wheat metabolism studies, the parent compound was rapidly hydrolysed to the metabolite M2 which was subsequently hydroxylated to the major metabolite M4 (≤ 20% of the TRRs in grain and ≤ 37% of the TRR in wheat straw) followed by conjugation (up to 28% of the TRR). Oxidation of the methyl-hydroxy function of M4 also lead to the corresponding carboxylic acid M6 which accounted for up to 14% of the TRRs in grain and less than 10% of the TRRs in straw. Therefore, while pinoxaden may be observed in forage harvested soon after application, there is no expectation of significant pinoxaden residues in mature grain and straw.

The major metabolites M4 (and its conjugates) and M6 in wheat were not identified in rotational crops. Metabolites M3, M10, M11 and the conjugates of M10 were found at (>10% of the TRRs) in all crop commodities at the 15-day, 29-30 day and 120-day plant-back intervals, but at low concentrations. Under field conditions, residues of these metabolites are expected to be low (i.e., <0.01 mg/kg), following uptake from soil.

The free and conjugated forms of the metabolite M4 represent the majority of the residues in primary crops. This is further supported by the results of the wheat and barley crop field trials where residues of free and conjugated M4 in wheat and barley grain accounted for up to 7-fold and 50-fold the residues of the metabolites M6 and M10, respectively. Therefore, the Meeting decided to define the residue for enforcement/monitoring for plant commodities as the free and conjugated forms of the metabolite M4.

Based on toxicity studies reviewed by the Meeting, the metabolite M4 was one of the major metabolites observed in rats. Further to this, toxicity studies on the metabolite M6 showed lower toxicity than pinoxaden. Therefore M6 is not considered relevant for the residue definition for dietary risk assessment. The Meeting decided to define the residue for dietary risk assessment for plant commodities as the free and conjugate metabolite M4.

In the future, should the use of pinoxaden be expanded to any crop other than a cereal crop, the Meeting recommends that additional plant metabolism studies be provided.

The metabolite M4, occurring as a major plant metabolite, was administered to lactating goats in the metabolism study. The predominant component identified in kidney and liver, the only matrices for which there was measurable radioactivity, was the unchanged metabolite M4. A laying hen metabolism study with M4 was not conducted.

In the livestock feeding studies, poultry and dairy cattle were both dosed with M4. While all matrices were analyzed for the metabolites M4 and M6, no quantifiable residues of these metabolites were observed in milk, eggs and all tissues collected from animals administered the highest dose tested. Being the major compound observed in metabolism and feeding studies, M4 could be included in the residue definition for enforcement as a marker compound. Since the analytical method is capable of analyzing M4, the Meeting agreed to define the residue for enforcement/monitoring and dietary intake for livestock commodities as the metabolite M4.

Neither the goat metabolism study nor the dairy cattle feeding study showed a partition of the metabolite M4 into the fat tissues or milk at any dose level. Similarly in the laying hen metabolism study and the poultry feeding study, the partitioning of the metabolite M4 into the fatty tissues and eggs was not observed. Since this metabolite did not sequester to fatty matrices in animals, the Meeting does not consider the residue fat soluble.

Definition of the residue for compliance with the MRLs and dietary intake for plant commodities: Sum of free and conjugated M4 (SYN 505164; *8-(2,6-Diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one*), expressed as pinoxaden equivalents.

Definition of the residue for compliance with the MRLs and dietary intake for animal commodities: M4 (SYN 505164; *8-(2,6-Diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one*), expressed as pinoxaden equivalents.

Results of supervised residue trials on crops

Cereal grains

Results from supervised field trials on wheat and barley conducted in Canada, USA and Europe were provided to the Meeting.

A total of 142 supervised trials were conducted in Canada, the USA, Germany, the Netherlands, United Kingdom, France, Italy, Spain, Switzerland and Greece on wheat (92) and barley (50). The GAP in Canada, the USA and Slovenia for cereal grains allows a single early post-emergence application at growth stages ranging from BBCH 13–39 at a rate of 0.06 kg ai/ha, with a PHI of 60 days for grain (PHI not specified on the Slovenia label). For the 2013 European trials, where grain samples, collected from trials conducted at 0.06 kg ai/ha, were analysed using the QuEChERS method, these residues were not considered in the MRL recommendation as they do not reflect the proposed residue definition for MRL compliance/enforcement.

Residues of total M4 (free and conjugated and expressed as parent equivalents) in wheat grain from 30 Canadian and USA independent trials and 26 European independent trials matching the Canadian and USA critical GAPs were: <0.01 (6), 0.01 (2), 0.02 (4), 0.04 (3), 0.05 (4), 0.06 (2), 0.07 (4), 0.08 (2), 0.10, 0.11 (6), 0.13 (4), 0.14 (2), 0.16 (2), 0.17, 0.18, 0.19, 0.22, 0.23, 0.29 (2), 0.31 (2), 0.35, 0.37, 0.38, 0.50, 0.66 mg/kg (n = 56).

Based on the combined residue data for wheat grain, the Meeting estimated a maximum residue level of 0.7 mg/kg, and an STMR of 0.10 mg/kg.

Residues of total M4 (free and conjugated and expressed as parent equivalents) in barley grain from 21 independent Canadian and USA trials and 17 independent European trials matching the

Canadian and USA critical GAPs were: <0.01, 0.02(3), 0.04 (4), 0.05 (4), 0.06, 0.07(4), 0.08(2), 0.10 (4), 0.12, 0.13, 0.14(2), 0.17 (3), 0.18, 0.19 (2), 0.32, 0.34, 0.36, 0.56 (2) mg/kg (n = 38).

Based on the combined residue data for barley grain, the Meeting estimated a maximum residue level of 0.7 mg/kg and an STMR of 0.09 mg/kg.

Animal feed items

Wheat and barley forage, hay and straw

Supervised field trials on wheat forage/whole plant, hay and straw and barley hay and straw were provided to the Meeting.

These trials were conducted in Canada, the USA, Germany, the Netherlands, United Kingdom, France, Italy, Spain, Switzerland and Greece on wheat and barley.

The GAP in Canada for cereal grains allows a single early post-emergence application at growth stages up to BBCH 37 at a rate of 0.06 kg ai/ha, with a grazing interval of 7 days for forage and PHIs of 30 days for hay and 60 days for straw.

In the USA, the GAP allows for a single early post-emergence application at growth stages up to BBCH 39 at a rate of 0.06 kg ai/ha, however, the forage can only be harvested for hay 30 days after application and the PHI for straw is 90 days.

While the GAP in Slovenia is the same as the Canadian and USA GAPs with applications permitted within growth stages BBCH 13-39, no grazing restrictions or PHIs for feed are specified.

Forage and whole plant of wheat

Residues of total M4 (free and conjugated expressed as parent equivalents) in wheat forage from 9 independent Canadian trials and wheat whole plant from 3 independent European trials, matching the Canadian critical GAP were: 0.24, 0.35, 0.40, 0.73, 1.27, 1.33, 1.48, 1.67, 1.94, 2.24, 2.38, 3.54 mg/kg (n = 12).

Based on the combined residue data from Canada and Europe for wheat forage and whole plant, the Meeting estimated a highest residue of 3.54 mg/kg and a median residue of 1.41 mg/kg.

Hay of wheat and barley

Average residues of total M4 (free and conjugated and expressed as parent equivalents) in wheat hay, as received, from 32 independent Canadian and USA trials matching the Canadian and USA critical GAPs were: <0.02(3), 0.04(2), 0.05(3), 0.06, 0.08, 0.11, 0.13 (2), 0.16, 0.19 (2), 0.20, 0.24, 0.26, 0.53, 0.62, 0.66, 0.73, 0.74, 0.82, 0.86 (2), 0.89, 1.22, 1.36, 1.44 mg/kg (n = 32).

Average residues of total M4 (free and conjugated expressed as parent equivalents) in barley hay, as received, from 20 independent Canadian and USA trials matching the Canadian and USA GAPs were: < 0.02, 0.02(3), 0.05(4), 0.11, 0.12, 0.14, 0.16, 0.24, 0.25, 0.29, 0.31(2), 0.48, 0.60, 0.72 mg/kg (n = 20).

Noting that hay of small cereal grains (wheat and barley) are very similar and difficult to distinguish in trade, and, residue populations for wheat and barley hay are not significantly different (Kruskal-Wallis), the Meeting decided to combine the residues (as received): < 0.02(4), 0.02(3), 0.04(2), 0.05(7), 0.06, 0.08, 0.11(2), 0.12, 0.13 (2), 0.14, 0.16(2), 0.19 (2), 0.20, 0.24(2), 0.25, 0.26, 0.29, 0.31(2), 0.48,0.53, 0.60, 0.62, 0.66, 0.72, 0.73, 0.74, 0.82, 0.86 (2), 0.89, 1.22, 1.36, 1.44 mg/kg (n = 52).

Straw of wheat and barley

Residues of total M4 (free and conjugated and expressed as parent equivalents) in wheat straw, as received, from 31 independent Canadian and USA trials and 26 independent European trials matching the Canadian and USA critical GAPs were: < 0.02(2), 0.04, 0.05(4), 0.06(2), 0.07(3), 0.08, 0.11(3), 0.12, 0.13, 0.17(2), 0.18, 0.19 (2), 0.20 (4), 0.24(3), 0.25(2), 0.29, 0.30, 0.32, 0.34(2), 0.35(2), 0.37, 0.38(2), 0.42(3), 0.43, 0.47, 0.62, 0.68, 0.77, 0.83, 0.89, 0.98, 1.08, 1.31 mg/kg (n = 57).

Residues of total M4 (free and conjugated and expressed as parent equivalents) in barley straw, as received, from 22 independent Canadian and USA trials and 18 independent European trials matching the Canadian and USA critical GAPs were: <0.02(3), 0.02, 0.05(5), 0.06, 0.07(4), 0.08, 0.10(5), 0.11, 0.12(6), 0.13, 0.14 (3), 0.17, 0.18, 0.20, 0.23, 0.24, 0.26, 0.29, 0.41, 0.44, 0.64 mg/kg (n = 40).

Similar to hay, noting that straw of small cereal grains (wheat and barley) are very similar and difficult to distinguish in trade, and, residue populations for wheat and barley straw are not significantly different (Kruskal-Wallis), the Meeting decided to combine the residues (as received): <0.02(5), 0.02, 0.04, 0.05(9), 0.06(3), 0.07(7), 0.08(2), 0.10(5), 0.11(4), 0.12(7), 0.13(2), 0.14(3), 0.17(3), 0.18(2), 0.19(2), 0.20(5), 0.23, 0.24(4), 0.25(2), 0.26, 0.29(2), 0.30, 0.32, 0.34(2), 0.35(2), 0.37, 0.38(2), 0.41, 0.42(3), 0.43, 0.44, 0.47, 0.62, 0.64, 0.68, 0.77, 0.83, 0.89, 0.98, 1.08, 1.31 mg/kg (n = 97).

As the residues of M4 (expressed as parent equivalents) were higher in hay (dry weight basis) compared to straw (dry weight basis), the Meeting estimated a maximum residue level for *wheat and barley straw and fodder* of 3 mg/kg (dry weight basis), a highest residue of 1.44 mg/kg and a median residue of 0.16 mg/kg, all based on wheat hay.

Fate of residues during processing

High temperature hydrolysis

No high temperature hydrolysis studies, simulating the degradation of the metabolite M4 during pasteurization, baking, brewing, boiling and sterilization were provided,

Processing

The Meeting received information on the fate of pinoxaden residues and its metabolites M2, M4 and M6 during the processing of wheat and barley grains.

Processing factors calculated for the processed commodities of the cereal grains are shown in the tables below. Processing factors, best estimates and STMR-Ps were calculated for M4.

Wheat

Commodity	Calculated Processing Factor	Best Estimate	STMR-P or median
Aspirated grain fractions	0.10, 0.16	0.13 (mean)	0.01
Unprocessed bran	1.20, 4.73, 4.38	4.38 (median)	0.44
Flour	0.15, 0.16, 0.21	0.16 (median)	0.02
Middlings	0.58, 0.72, 2.75	0.72 (median)	0.07
Shorts	0.93, 1.0	0.96 (mean)	0.10
Germ	0.21, 0.35, 0.58	0.35 (median)	0.04
Low grade meal (toppings)	1.21	1.21	0.12
Wholemeal flour	1.08	1.08	0.11
Wholemeal bread	0.58	0.58	0.06

Barley

Commodity	Calculated Processing Factors	Best Estimate	STMR-P or median
Pearled barley	1.25, 0.85, 0.48	0.48 (median)	0.04
Flour	0.50, 0.42	0.46 (mean)	0.04
Unprocessed bran	2.65, 0.77	1.71 (mean)	0.15
Malt (after drying)	1.20	1.20	0.11
Malt sprouts	0.47	0.47	0.04
Malt (before brewing)	1.17	1.17	0.11
Beer	0.13	0.13	0.01

As the residue concentrations of M4 in all processed commodities are not higher than the estimated maximum residue levels for wheat and barley grain, separate maximum residue levels will not be estimated for any of the cereal grain processed commodities.

Residues in animal commodities

Farm animal feeding studies

The Meeting received information on the residue levels arising in tissues and milk when three groups of dairy cows were fed with a diet containing 1.11, 3.01, and 10.12 mg of M4/kg feed for 29–30 consecutive days.

In milk, liver, kidney, muscle and fat, no quantifiable (<LOQ) residues of M4 or M6 were observed in the 10× treatment group. Hence, samples from the low and mid dose experiments were not analyzed.

The Meeting also received information on the residue levels arising in tissues and eggs when groups of laying hens were fed with a diet containing M4 at rates of 0.5 mg/kg feed, 1.5 mg/kg feed and 5.0 mg/kg feed per day for 28 consecutive days.

In eggs, muscle, liver, and fat, no quantifiable (<LOQ) residues of M4 or M6 were detected in the 10x treatment group. Because of this, no samples from the low and mid doses were analyzed.

Estimated dietary burdens of farm animals

Maximum and mean dietary burden calculations for pinoxaden are based on the feed items evaluated for cattle and poultry as presented in Annex 6. The calculations were made according to the livestock diets from Australia, the EU, Japan and US-Canada in the OECD feeding table.

The foliar application of pinoxaden to wheat and barley resulted in residues in the following feed items: wheat forage/whole plant, wheat and barley hay, straw and grain (including aspirated grain fractions, bran, meal and milled by-products). Based on the named feed items, the calculated maximum animal dietary burden for dairy or beef cattle was in Australia, followed by EU and US-Canada. For poultry broiler or layer, the calculated maximum dietary burden was in EU, followed by US-Canada and Australia.

	Livestock dietary burden, M4 (expressed as parent equivalents), ppm of dry matter							
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	0.49	0.28	3.2	1.3	14.2	5.6	0.32	0.32
Dairy cattle	2.8	1.1	2.8	1.1	8.5	3.4	0	0
Poultry - broiler	0.25	0.25	0.10	0.10	0.10	0.10	0.02	0.02
Poultry-layer	0	0	1.4[A]	0.56[B]	0	0	0	0

[A] Suitable for MRL estimates for eggs, meat, fat and edible offal of poultry

[B] Suitable for STMR estimates for eggs, meat, fat and edible offal of poultry

Animal commodities maximum residue level estimation

As the feeding levels from the dairy cattle feeding study did not address the maximum dietary burdens for cattle in Australia, the Meeting could not estimate MRLs for M4 (expressed in parent equivalents) for milk, meat from mammals, mammalian fat and edible offal (mammalian).

As there were no quantifiable residues of M4 detected in eggs, muscle, liver and fat collected from laying hens dosed 5 mg M4/kg feed (ca. 3-fold the maximum dietary burden in poultry (layer)), the Meeting estimated maximum residue levels of M4, expressed as parent equivalents, of 0.02* mg/kg for eggs and 0.02* mg/kg for edible offal, meat and fats of poultry. The HRs and STMRs for eggs, edible offal, meat and fat were each 0.02 mg/kg.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IESTI and IEDI assessments.

Definition of the residue for compliance with the MRLs and dietary intake for plant commodities: Sum of free and conjugated M4 (SYN 505164; *8-(2,6-Diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one*), expressed as pinoxaden.

Definition of the residue for compliance with the MRLs and dietary intake for animal commodities: M4 (SYN 505164; *8-(2,6-Diethyl-4-hydroxymethyl-phenyl)-9-hydroxy-1,2,4,5-tetrahydro-pyrazolo[1,2-d][1,4,5]oxadiazepin-7-one*), expressed as pinoxaden.

The residue is not fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The International Estimated Dietary Intakes (IEDIs) of pinoxaden were calculated for the 17

GEMS/Food cluster diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3 to the 2015 Report). The ADI is 0–0.1 mg/kg bw and the calculated IEDIs were 0–1% of the maximum ADI. The Meeting concluded that the long-term exposure to residues of pinoxaden resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term dietary exposure

The ARfD for pinoxaden is 0.3 mg/kg bw. The International Estimate of Short Term Intake (IESTI) for pinoxaden were calculated for the food commodities for which STMRs or HRs were estimated by the present Meeting and for which consumption data were available. The results are shown in Annex 4 of the 2016 JMPR Report. The IESTIs were 1% of the ARfD for the general population including children. The Meeting concluded that the short-term dietary exposure to residues of pinoxaden, from the uses that have been considered by the present Meeting, is unlikely to present a public health concern.