5.19 PENDIMETHALIN (292)

TOXICOLOGY

Pendimethalin is the ISO-approved common name for *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine (IUPAC), with the CAS number 040487-42-1. Pendimethalin is a selective herbicide belonging to the chemical class of dinitroanilines.

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

All critical studies complied with GLP and were conducted in accordance with relevant national or international test guidelines, unless otherwise stated.

Biochemical aspects

In rats, orally administered radiolabelled pendimethalin was more than 57% absorbed from the gastrointestinal tract and rapidly excreted, independent of dose level. The excretion of radioactivity was similar for both sexes; 70% of the radioactivity was excreted in the faeces and about 20% in the urine within 24 hours post-treatment. After 96 hours, the residual radioactivity in the soft tissues accounted for 0.2% of the radioactive dose. After a single oral gavage dose, pendimethalin was not detectable in the plasma even at the earliest time point of 1 hour, although its metabolites were detected. Thus, a liver first-pass effect with a complete, or nearly complete, biotransformation during absorption and liver passage can be assumed. The T_{max} for metabolites was 8 hours.

The biotransformation pathway includes oxidation, reduction and cyclization of pendimethalin. The transformation steps are (a) oxidation of the alkyl side-chains (methyl and/or 1-ethylpropyl group), which results in hydroxyl and/or carboxyl groups, (b) reduction of one or two nitro groups to amine groups and (c) cyclization to a benzimidazole heterocycle. The metabolite patterns in faecal extracts were qualitatively similar, but quantitatively different, in males and females. About 88% of orally absorbed pendimethalin was excreted in bile. In total, 23 metabolites, predominantly glucuronide conjugates, were detected in bile; some of these metabolites were chemically characterized.

In an in vitro study, pendimethalin was extensively metabolized by liver microsomes of dogs, rabbits, mice, rats and humans; no unique human metabolite was detected.

Toxicological data

Pendimethalin has low acute toxicity when administered orally, dermally or by inhalation to rats. The acute oral LD_{50} was greater than 4665 mg/kg bw, the dermal LD_{50} was greater than 5000 mg/kg bw and the inhalation LC_{50} was greater than 6.73 mg/L (4-hour exposure; nose only). Pendimethalin was not irritating to the skin or the eyes of rabbits. Pendimethalin has skin sensitizing properties at comparatively high concentrations in the guinea-pig maximization test. Pendimethalin was phototoxic in vitro.

In short-term and long-term studies in mice, rats and dogs, the main target organs of pendimethalin were the liver (increased weight with histopathological changes and changes in serum alkaline phosphatase) in all species tested and the thyroid (increased weight, histopathological changes) in rats.

In a 30-day dietary study in which rats were administered pendimethalin in the diet at 0, 800, 1600 or 3200 ppm (equal to 0, 85.4, 163 and 338 mg/kg bw per day for males and 0, 86.2, 168 and 333 mg/kg bw per day for females, respectively), the NOAEL was 3200 ppm (equal to 333 mg/kg bw per day), the highest dose tested.

In a 90-day dietary study in rats given pendimethalin at 0, 100, 500 or 5000 ppm (equivalent to 0, 8.3, 41.3 and 413 mg/kg bw per day, respectively), the NOAEL was 500 ppm (equivalent to 41.3 mg/kg bw per day), based on a marginal increase in kidney weight (males) and a decrease in uterus/ovary weight at 5000 ppm (equivalent to 413 mg/kg bw per day).

In a 90-day toxicity study in dogs administered pendimethalin at a dose level of 0, 62.5 (diet), 250 or 1000 mg/kg bw per day (gavage), the NOAEL was 1000 mg/kg bw per day, the highest dose tested.

In a 2-year toxicity study in dogs given pendimethalin at a dose level of 0, 12.5, 50 or 200 mg/kg bw per day in gelatine capsules, the NOAEL was 12.5 mg/kg bw per day, based on elevated alkaline phosphatase levels and histopathological findings (bile stasis, chronic inflammation, biliary hyperplasia) in the liver at 50 mg/kg bw per day.

In an 18-month dietary toxicity and carcinogenicity study in mice administered pendimethalin at a dose level of 0, 100, 500 or 5000 ppm (equivalent to 0, 15, 75 and 750 mg/kg bw per day, respectively), the NOAEL was 5000 ppm (equivalent to 750 mg/kg bw per day), the highest dose tested. No treatment-related effects on tumour incidence were observed in this study.

In a 2-year toxicity and carcinogenicity study in rats administered pendimethalin in the diet at a dose level of 0, 100, 500 or 5000 ppm (equal to 0, 3.8, 19 and 195 mg/kg bw per day for males and 0, 4.7, 24 and 260 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 19 mg/kg bw per day), based on clinical signs, lower body weight gain and decreased feed consumption at 5000 ppm (equal to 195 mg/kg bw per day). Females also had increased terminal absolute and relative liver and thyroid/parathyroid weights at 5000 ppm. Treatment-related increases in follicular cell adenomas in the thyroid were observed at the high dose in both sexes.

In another 2-year dietary study conducted to investigate the effects of chronic dietary administration of pendimethalin on the function and structure of male rat thyroid at 0, 1250, 2500, 3750 and 5000 ppm (equivalent to 0, 62.5, 125, 187.5 and 250 mg/kg bw per day, respectively), the systemic toxicity NOAEL was 1250 ppm (equivalent to 62.5 mg/kg bw per day), based on eosinophilic and basophilic foci, hepatocellular hypertrophy, hepatocellular intracytoplasmic eosinophilic inclusions and increased relative liver weight at 2500 ppm (equivalent to 125 mg/kg bw per day). The NOAEL for tumorigenicity was 3750 ppm (equivalent to 187.5 mg/kg bw per day), based on an increased incidence of thyroid follicular cell adenomas at 5000 ppm (equivalent to 250 mg/kg bw per day).

A number of additional special studies were performed to determine the effect of pendimethalin on thyroid in rats.

In a 14-day study in male rats, pendimethalin was administered at dietary dose levels of 0, 100 and 5000 ppm (equivalent to 0, 5 and 250 mg/kg bw per day, respectively). The NOAEL for thyroidal effects was 100 ppm (equivalent to 5 mg/kg bw per day), based on hypothyroidism, as defined by a decrease in serum T_4 and triiodothyronine (T_3) levels, an increase in serum TSH level and a significant increase in the uptake of ^{131}I at 5000 ppm, but with no change in serum reverse T_3 level. However, there was no effect on the organification of ^{131}I or the percentage of ^{131}I incorporated into monoiodotyrosine, diiodotyrosine or T_4 in rats. This suggests that pendimethalin does not affect the synthesis of thyroid hormones and is therefore not a primary goitrogen.

When pendimethalin was administered to male rats for 14 days at a dietary concentration of 0, 100 or 5000 ppm (equivalent to 0, 5 and 250 mg/kg bw per day, respectively) to assess the influence of the test substance on biliary excretion and hepatic metabolism of T_4, decreased serum total T_3/T_4 and increased serum TSH concentration were observed at 5000 ppm. The 100 ppm level was without effect. Together with previous results indicating that pendimethalin had no direct effect on thyroid hormone synthesis, it can be judged that the effects in this study were induced via the classic secondary mechanism of TSH stimulation from catabolism of thyroid hormones.

In a 4-week thyroid function study in male rats, pendimethalin was administered at dietary dose levels of 0, 500 and 5000 ppm (equal to 0, 31 and 292 mg/kg bw per day, respectively) for a period of 28 days, followed by a recovery period for another 28 days. The changes observed in the study were decreased serum levels of T_3 and T_4 throughout the 4-week treatment period and a slight elevation of TSH after 4 weeks of dietary treatment of male rats with pendimethalin at the high dose of 5000 ppm. This level was also associated with a marked depression of body weight gain and elevated thyroid weights, but there was no effect on pituitary weights. Histomorphometric analysis demonstrated an increase in follicular cell height and a decrease in colloid area at 5000 ppm. Ultrastructural changes, including rough endoplasmic reticulum, large prominent Golgi apparatus with small granules, numerous colloid droplets and large mitochondria, consistent with mild to moderate TSH stimulation were observed at 5000 ppm. After a 4-week recovery period, reversal of the histomorphometric changes in the follicular cells occurred, as well as a return to control levels of T_3 and T_4 and thyroid weights.

In a 92-day investigative study of the effect of pendimethalin on thyroid function in rats, pendimethalin was administered at dietary dose levels of 0, 100 and 5000 ppm (equal to 0, 5 and 245 mg/kg bw per day, respectively). Treatment of rats at 5000 ppm resulted in decreased blood T_3 and T_4 levels and an increase in TSH level, as well as increased absolute and relative thyroid weights and hypertrophy of follicular cells of this gland.

All these findings support the hypothesis of a decrease in thyroid hormones due to enhanced liver metabolism induced by pendimethalin. The secondary increase in TSH levels is likely responsible for the slight increase in the incidence of thyroid follicular cell adenomas in rats following 2 years of dietary treatment with pendimethalin at a dose of 5000 ppm. This supports a well-established mode of action for follicular cell adenomas in rats, which is not relevant for humans.

The Meeting concluded that pendimethalin is not carcinogenic in rats and mice and that the thyroid adenomas observed in rats occur by a mode of action that is not relevant to humans.

Pendimethalin was tested for genotoxicity in an adequate range of in vitro and in vivo assays. No evidence of genotoxicity was found.

The Meeting concluded that pendimethalin is unlikely to be genotoxic.

In view of the lack of genotoxicity, the absence of carcinogenicity in rats and mice and the fact that the follicular cell adenomas of the thyroid observed in rats occur by a mode of action that is not relevant to humans, the Meeting concluded that pendimethalin is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation reproductive toxicity study in rats, pendimethalin was administered in the diet at target dose levels of 0, 500, 2500 and 5000 ppm (equal to 0, 30, 150 and 296 mg/kg bw per day for males and 0, 39, 195 and 388 mg/kg bw per day for females, respectively). The NOAEL for parental toxicity was 500 ppm (equal to 39 mg/kg bw per day), based on reduced feed consumption and body weight/body weight gain in dams at 2500 ppm (equal to 195 mg/kg bw per day). The NOAEL for offspring toxicity was 500 ppm (equal to 39 mg/kg bw per day), based on significantly reduced body weight and body weight gain in offspring at 2500 ppm (equal to 195 mg/kg bw per day). The reproductive toxicity NOAEL was 5000 ppm (equal to 296 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rats, pendimethalin was administered orally by gavage from day 6 through day 15 of gestation at a dose of 0, 125, 250 or 500 mg/kg bw per day. The NOAEL for both maternal toxicity and embryo/fetal toxicity was 500 mg/kg bw per day, the highest dose tested.

In a study of thyroid function during development in rats, pendimethalin was administered in the diet in concentrations that were adjusted to obtain dose levels of 0, 31, 62 and 186 mg/kg bw per day from gestation day 6 through postnatal day 21. Fetuses and pups were shown to be less sensitive than dams to thyroid hormone changes, as thyroid hormones in fetuses and postnatal day 4 pups of

exposed dams remained generally unaltered, even when the dams showed significantly decreased T_4 levels. Serum T_4 levels of pups were affected only after exposure via the diet in addition to the milk, albeit substantially less than in dams.

In a developmental toxicity study in rabbits, pendimethalin was administered orally by gavage from day 6 through day 18 of gestation at a dose level of 0, 15, 30 or 60 mg/kg bw per day. The NOAEL for maternal toxicity was 30 mg/kg bw per day, based on the increased incidences of anorexia and adipsia observed during treatment at 60 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 30 mg/kg bw per day, based on skeletal variations observed at 60 mg/kg bw per day.

The Meeting concluded that pendimethalin is not teratogenic.

In an acute neurotoxicity study in rats, pendimethalin was administered orally by gavage at a dose level of 0, 100, 300 or 1000 mg/kg bw. This administration resulted in signs of neurotoxicity, which were considered to be secondary to systemic toxicity. The NOAEL was 100 mg/kg bw, based on a number of clinical signs observed in both sexes on study day 0 at 300 mg/kg bw.

In a 90-day neurotoxicity study in rats, pendimethalin was administered orally at a dietary dose level of 0, 600, 1800 or 5400 ppm (equal to 0, 42, 127 and 387 mg/kg bw per day for males and 0, 50, 152 and 423 mg/kg bw per day for females, respectively). The systemic toxicity NOAEL was 600 ppm (equal to 50 mg/kg bw per day), based on decreased body weight gain and feed consumption and changes in clinical chemistry and haematological parameters in females at 1800 ppm (equal to 152 mg/kg bw per day). The NOAEL for neurotoxicity was 5400 ppm (equal to 387 mg/kg bw per day), the highest dose tested.

The Meeting concluded that pendimethalin is not neurotoxic.

In a 4-week immunotoxicity study in female rats administered pendimethalin in the diet at a concentration of 0, 500, 1000 or 3000 ppm (equal to 0, 38, 72 and 276 mg/kg bw per day, respectively), the NOAEL for both general toxicity and immunotoxicity was 3000 ppm (equal to 276 mg/kg bw per day), the highest dose tested.

The Meeting concluded that pendimethalin is not immunotoxic.

Toxicological data on metabolites and/or degradates

Several metabolites, including plant metabolites and a rat and soil metabolite, were tested for genotoxicity.

M455H025 (Reg. No. 4110480; rat and plant metabolite)

M455H025 ({4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrophenyl}methanol) was negative in the Ames test and equivocal in an in vitro micronucleus assay in V79 cells with and without metabolic activation. An in vivo micronucleus test up to the limit dose did not result in an increase in micronucleus formation. The Meeting concluded that M455H025 is unlikely to be genotoxic in vivo.

The dietary exposure level of M455H025 from current uses (1.3 µg/kg bw per day) does not exceed the TTC (1.5 µg/kg bw per day) for a Cramer class III compound.

M455H066 (Reg. No. 4118469; plant metabolite)

M455H066 (*N*-(1-ethyl-2-hydroxy-propyl)-2,6-dinitro-3,4-xylidine) was negative in the Ames test, but resulted in an increase in micronuclei in an in vitro micronucleus assay in V79 cells with and without metabolic activation. An in vivo micronucleus test up to the limit dose did not result in an increase in micronucleus formation. The Meeting concluded that M455H066 is unlikely to be genotoxic in vivo.

M455H058 (Reg. No. 4309702; plant metabolite)

M455H058 was negative in the Ames test, but resulted in an increase in micronuclei in an in vitro micronucleus assay in V79 cells without metabolic activation. An in vivo micronucleus test up to 500 mg/kg bw did not result in an increase in micronucleus formation. The Meeting concluded that M455H058 is unlikely to be genotoxic in vivo.

Reg. No. 5916419 (rotational crop metabolite)

Reg. No. 5916419 was negative in the Ames test and in an in vitro micronucleus assay in V79 cells with and without metabolic activation. The Meeting concluded that Reg. No. 5916419 is unlikely to be genotoxic.

M455H001 (Reg. No. 4108474; rat and soil metabolite)

M455H001 (2-methyl-3,5-dinitro-4-(pentan-3-ylamino)benzoic acid) was negative in the Ames test and in an in vitro mouse lymphoma test, but resulted in an increase in chromosomal aberrations in an in vitro chromosomal aberration assay with metabolic activation. An in vivo micronucleus test up to the limit dose did not result in an increase in micronucleus formation. The Meeting concluded that M455H001 is unlikely to be genotoxic in vivo.

M455H029 (major residue in ruminant liver and kidney)

M455H029 (1-(1-ethylpropyl)-5,6-dimethyl-7-nitro-1*H*-benzimidazole) was not tested for genotoxicity. Quantitative structure–activity relationship (QSAR) analysis suggested a plausible alert for mutation in an Ames test. The moiety responsible was an aromatic nitro grouping. Pendimethalin exhibited the same alert. As pendimethalin was negative when tested in the Ames test, the Meeting concluded that M455H029 is unlikely to be mutagenic.

The dietary exposure level of M455H029 from current uses (0.3 µg/kg bw per day) does not exceed the TTC (1.5 µg/kg bw per day) for a Cramer class III compound.

M455H030 (found in radish roots after crop rotation)

M455H030 was not tested for genotoxicity. It is the glucuronide of metabolite Reg. No. 5916419, which tested negative for gene mutation (Ames) and in vitro chromosomal aberration (in vitro micronucleus test). Consequently, this metabolite is negative for genotoxicity and thus adequately tested. Sugar conjugates (especially *O*-glycosyls) are likely to be cleaved in the intestinal tract. As a consequence, the respective parent metabolite should be considered relevant.

The dietary exposure level of M455H030 from current uses (0.1 µg/kg bw per day) does not exceed the TTC (1.5 µg/kg bw per day) for a Cramer class III compound.

Human data

From reports on health records of manufacturing plant personnel, no adverse health effects were noted during pendimethalin production, transportation, formulation or packaging.

A number of reports on intentional poisoning in humans available in the literature showed dose-related gastrointestinal signs and symptoms.

Epidemiological studies

Several epidemiological studies that reviewed pesticide use and associations with overall health impact are available based on the AHS cohort. Out of six evaluations of one cohort study, various associations with increased risk of different types of cancer with varying degrees of confidence were

noted for pendimethalin. These associations need to be balanced against the fact that they were seen from evaluations of a single cohort. Although data were stratified for confounders, it needs to be kept in mind that participants were also exposed to additional compounds.

Other studies

Several publications were found in the published literature that reported in vitro investigations of pendimethalin's endocrine activity. However, the data are not in line with the available higher-tier studies of pendimethalin in rats and rabbits, which did not provide evidence for a human-relevant endocrine-related risk.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.1 mg/kg bw, derived from a NOAEL of 12.5 mg/kg bw per day from the 2-year study of toxicity in dogs, on the basis of elevated alkaline phosphatase levels and histopathological findings in the liver at 50 mg/kg bw per day. A safety factor of 100 was applied.

The Meeting established an ARfD of 1 mg/kg bw, derived from a NOAEL of 100 mg/kg bw from an acute neurotoxicity study in rats for a number of clinical signs observed in both sexes at 300 mg/kg bw. A safety factor of 100 was applied.

A toxicological monograph was prepared.

Levels relevant to risk assessment of pendimethalin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	5 000 ppm, equivalent to 750 mg/kg bw per day[b]	–
		Carcinogenicity	5 000 ppm, equivalent to 750 mg/kg bw per day[b]	–
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	500 ppm, equal to 19 mg/kg bw per day	5 000 ppm, equal to 195 mg/kg bw per day
		Tumorigenicity	500 ppm, equal to 19 mg/kg bw per day	5 000 ppm, equal to 195 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	5 000 ppm, equal to 296 mg/kg bw per day[b]	–
		Parental toxicity	500 ppm, equal to 39 mg/kg bw per day	2 500 ppm, equal to 195 mg/kg bw per day
		Offspring toxicity	500 ppm, equal to 39 mg/kg bw per day	2 500 ppm, equal to 195 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	500 mg/kg bw per day[b]	–
		Embryo and fetal	500 mg/kg bw per day[b]	–

Species	Study	Effect	NOAEL	LOAEL
		toxicity		
	Acute neurotoxicity study[c]	Neurotoxicity	1 000 mg/kg bw[b]	–
		Toxicity	100 mg/kg bw	300 mg/kg bw
	Ninety-day neurotoxicity study[a]	Neurotoxicity	5 400 ppm, equal to 387 mg/kg bw[b]	–
Rabbit	Developmental toxicity study[c]	Maternal toxicity	30 mg/kg bw per day	60 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	60 mg/kg bw per day
Dog	Two-year study of toxicity[d]	Toxicity	12.5 mg/kg bw per day	50 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Capsule administration.

Acceptable daily intake (ADI)

0–0.1 mg/kg bw

Acute reference dose (ARfD)

1 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 pendimethalin

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly and > 57% absorbed; T_{max} 8 h for metabolites
Dermal absorption	Poorly absorbed
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	70% excreted in the faeces and about 20% in the urine within 24 h
Metabolism in animals	Extensively and rapidly metabolized via oxidation, reduction and cyclization
Toxicologically significant compounds in animals and plants	Pendimethalin
Acute toxicity	
Rat, LD_{50}, oral	> 4 665 mg/kg bw

Rat, LD_{50}, dermal	> 5 000 mg/kg bw
Rat, LC_{50}, inhalation	> 6.73 mg/L
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Non-irritating
Guinea-pig, dermal sensitization	Weakly sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Liver, thyroid (rat and dog)
Lowest relevant oral NOAEL	12.5 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver; thyroid
Lowest relevant NOAEL	19 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats; thyroid adenomas in rats not relevant to humans[a]
Genotoxicity	
	No evidence of genotoxicity[a]
Reproductive toxicity	
Target/critical effect	No reproductive effects; reduced body weight/body weight gain in offspring; reduced feed consumption and body weight/body weight gain in dams
Lowest relevant parental NOAEL	30 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	30 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	296 mg/kg bw per day, highest dose tested (rat)
Developmental toxicity	
Target/critical effect	Skeletal variations; anorexia and adipsia in dams
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	1 000 mg/kg bw, highest dose tested (rat)
	Systemic toxicity NOAEL: 100 mg/kg bw
Subchronic neurotoxicity NOAEL	387 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity NOAEL	276 mg/kg bw per day, highest dose tested (rat)
Human data	
Occupational	No effects reported in manufacturing workers
Cancer	Various associations of pendimethalin exposure with increased risk of different types of cancer with varying degrees of confidence were found in a single cohort study

Non-cancer health effects	No associations of pendimethalin exposure with increased likelihood of developing a wide variety of adverse non-cancer health effects have been reported

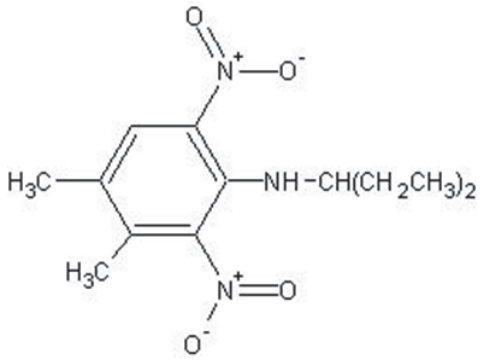
[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.1 mg/kg bw	Two-year toxicity study (dog)	100
ARfD	1 mg/kg bw	Acute neurotoxicity study (rat)	100

RESIDUE AND ANALYTICAL ASPECTS

Pendimethalin is a selective herbicide used to control most annual grasses and certain broadleaf weeds in several arable perennial crops, such as fruits and vegetables, cereals, pulses and oilseeds, root crops and ornamentals. Its primary mode of action is to prevent plant cell division and elongation in susceptible species by inhibition of microtubule formation. At the 47th Session of the CCPR (2015) the compound was scheduled for the evaluation as a new compound for toxicology and residues by the 2016 JMPR.



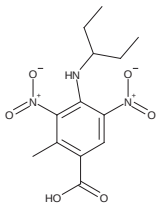
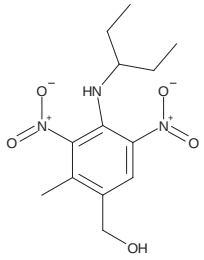
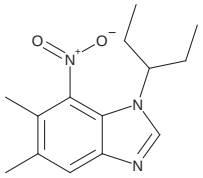
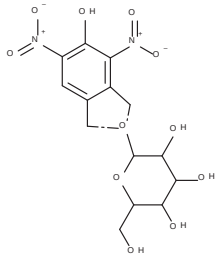
The IUPAC and CA name of pendimethalin is N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidine.

The physical-chemical properties of pendimethalin indicate that the substance is semi-volatile, which was confirmed in specific studies. After application, a short- to medium-range transport to nearby fields was demonstrated evaporation and resorption.

In aqueous solution photolysis was observed with half-life of less than a week. The octanol-water partition coefficient was measured at log P_{ow} = 5.4.

Pendimethalin radioactive labelled either in the phenyl- or 4-methyl-moiety were used in the metabolism and environmental fate studies.

The following abbreviations are used for the metabolites discussed below:

M455H001	2-methyl-3,5-dinitro-4-(pentan-3-ylamino)benzoic acid	
M455H025	{4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrophenyl}methanol	
M455H029	1-(1-ethylpropyl)-5,6-dimethyl-7-nitro-1*H*-benzimidazole	
M455H030	na	

na: It was not possible to assign a IUPAC name because the displayed generic structure represents more than one possible structure

Plant metabolism

The Meeting received plant metabolism studies for pendimethalin following foliar application of ^{14}C-phenyl or ^{14}C-4-methyl-radiolabelled active substance to onions, sweet corn, lettuce, carrots, potatoes and wheat.

For onions the metabolism of pendimethalin was investigated in the field with the ^{14}C-phenyl-label. Onions received a post-emergence treatment at the two-leaf-stage (BBCH 12) equivalent to 3.0 kg ai/ha. Samples of bulbs were collected 77 days after treatment.

In the samples the TRR level was 0.03 mg eq/kg. Approximately 78% of the TRR was extracted using methanol:water. The only compound identified was parent pendimethalin, representing 8% of the TRR (0.002 mg eq/kg). The remaining radioactivity was distributed into multiple analytical peaks each too low for identification.

For sweet corn, ^{14}C-phenyl-pendimethalin was applied at rates of 2.24 kg ai/ha either pre-emergence or at the 4-leaf stage 14 days later. In both plots, samples of plants (pre-emergence: 30 and 60 DAT, post-emergence: 14, 30 and 60 DAT)) as well as stalks, husks and cobs with grain (pre-emergence: 91 DAT, post-emergence: 81 DAT) were collected.

Highest TRR levels found were 2.75 mg eq/kg in whole plant samples collected 14 days after the post-emergence application. For samples of whole plants, stalks+husks and cobs+grain collected later, TRR levels following pre- and post-emergence application were in the same concentration range amounting 0.18–0.42 mg eq/kg, 0.22–0.26 mg eq/kg and 0.017–0.02 mg eq/kg, respectively.

The extraction rates of radioactivity were 71–72% for whole plants, 63% for stalks+husks and 50% for cobs+grain, using chloroform, methanol:water, enzyme treatment and 6N HCl hydrolysis. Further investigation on the composition of residues was performed for whole plant and stalks+husks samples. The only compound identified was parent pendimethalin present at 0.6–2.4% of the TRR. The remaining radioactivity remained unidentified and was characterised as more polar than the parent.

In a second study on sweet corn ^{14}C-4-methyl-pendimethalin was applied to plants of approximately 20–25cm height with a single treatment equivalent to 1.7 kg ai/ha. After treatment, samples of immature plants (14 and 42 DAT) as well as fodder, cobs with grain and grain samples (84 DAT) were collected.

TRR levels in whole plants collected two weeks after treatment were 3.2 mg eq/kg, but quickly declined to 0.02 mg eq/kg (42 DAT) and 0.04 mg eq/kg in fodder (84 DAT). In cobs without grain and in grain no radioactivity above the LOQ of 0.01 mg eq/kg was found.

Identification of radioactivity was performed for the 14 DAT whole plant samples in the methanol extract, indicating pendimethalin as the main residue (~6% TRR, 0.12 mg eq/kg). In addition, the minor metabolites CL217146 (~2% TRR, 0.04 mg eq/kg) and M445H025 (~3% TRR, 0.06 mg eq/kg) were found.

For lettuce ^{14}C-phenyl-pendimethalin was applied at a rate equivalent to 1.6 kg ai/ha to bare soil directly before transplanting. Young (27 DAT) and mature (48 DAT) lettuce plant were collected for analysis of their residues.

TRR levels found in lettuce were 0.3 mg eq/kg for the young and 0.15 mg eq/kg for the mature plants. In both samples pendimethalin was the only identified compound amounting 40% of the TRR (0.12 mg eq/kg) after 27 days and declined to 14% TRR (0.02 mg eq/kg) at maturity (48 DAT). Subsequent enzymatic treatment was performed, showing that the incorporation of radioactivity into carbohydrates increased from 8.6% TRR (0.025 mg eq/kg) to 34% TRR (0.05 mg eq/kg). From the remaining radioactivity 26–39% of the TRR were characterized as polar, while 7.4–14% remained unextracted.

Carrots were treated with ^{14}C-phenyl-pendimethalin at the 3-leaf stage (BBCH 13) with a single broadcast spraying equivalent to 2.0 kg ai/ha. Mature plants were harvested at 57 DAT and separated into leaves and roots.

TRR levels found were 3.1 mg eq/kg in carrot leaves and 0.23 mg eq/kg in the roots. 71–75% of the radioactivity could be extracted by methanol and water.

Identification of the radioactivity showed parent pendimethalin as the major residue, representing 29% of the TRR in leaves (0.88 mg eq/kg) and 16% TRR in roots (0.038 mg eq/kg). In leaves, minor amounts of M455H025 were detected (4.6% TRR, 0.14 mg eq/kg), but not in roots. Following subsequent enzymatic treatment, most of the radioactivity in roots was characterized as incorporated into carbohydrates (63% TRR, 0.15 mg eq/kg), which was also observed in the leaves but at a lower amount (3.7% TRR, 0.12 mg eq/kg).

The metabolism of pendimethalin in potatoes was investigated using ^{14}C-phenyl-labelled active substance. Plants of approximately 15 cm height were treated once with an application rate equivalent to 1.7 kg ai/ha. Foliage was collected directly after treatment (0 DAT) while mature tubers were collected after 109 days.

TRR levels in foliage were 60 mg eq/kg, while in mature potato tubers only 0.062 mg eq/kg was found. Solvent extraction using water/methanol/chloroform released 99% of the TRR from the foliage and 42% from the tubers. Enzyme treatment and 1N HCl reflux released additional 49% TRR. The identification showed nearly the entire radioactivity being present as pendimethalin in the foliage directly after treatment. In the tubers parent pendimethalin was the only residue identified at 2.8% TRR (0.002 mg eq/kg). The major part of the remaining radioactivity resolved into multiple minor chromatographic peaks each too low for identification.

Wheat plants were treated with ^{14}C-phenyl-pendimethalin at growth stage BBCH 16 with a single foliar application equivalent to 2.0 kg ai/ha. Samples of wheat forage were taken 27 days after treatment at BBCH 39 and parts of the samples were dried to hay. Mature wheat plants were harvested 73 DAT and separated into straw, chaff and grain.

TRR levels found in the various matrices were 17 mg eq/kg for forage and 689 mg eq/kg for hay (both 27 DAT), 60 mg eq/kg in straw, 2.3 mg eq/kg in chaff and 0.47 mg eq/kg in grain (all 73 DAT). Solvent extraction using methanol and water released 70–74% of the TRR from forage/hay, 65% TRR from straw, 56% TRR from chaff and only 24% TRR from the grain. Following additional enzymatic and acid/base hydrolysis, unextracted residues were reduced to < 7.4% TRR.

Overall, parent pendimethalin was detected in all matrices but it was highly metabolised, amounting 1.3–5.2% of the TRR in forage, hay, straw and chaff. In the grain only 0.8% of the TRR (0.004 mg eq/kg) were recovered as pendimethalin, which was the only identified compound in this matrix.

In addition to the parent, the isomeric mixtures M455H002 to M455H003 and M455H005 to M455H008 were only found in straw and chaff (0.7–1.5% TRR, 0.023–0.47 mg eq/kg) while M455H009/M455H010 were present in forage and hay (1.1–3.4% TRR, 0.025–2.0 mg eq/kg).

In the grain the major part of the radioactivity was incorporated into carbohydrates, amounting 59% of the TRR (0.28 mg eq/kg), which was also observed in chaff (4.9% TRR, 0.11 mg eq/kg). The unidentified radioactivity was primarily characterized to be highly (5.0–19% TRR) or medium polar (26–59% TRR).

Three confined rotational crop studies for pendimethalin were submitted.

In the first study ^{14}C-phenyl-pendimethalin was applied under field conditions to bare soil at a rate equivalent to 2.0 kg ai/ha. Lettuce, radish and wheat were planted in the treated soil 30, 120 and 365 days after test substance application. TRR levels were highest in the shortest plant-back interval. From 30 to 365 days PBI TRR levels declined from 0.18 to 0.017 mg eq/kg for lettuce, 0.082 to 0.006 mg eq/kg for radish tops, 0.13 to 0.033 mg eq/kg for radish roots, 0.33 to 0.039 mg eq/kg for wheat forage, 2.3 to 0.21 mg eq/kg for wheat hay, 1.8 to 0.42 mg eq/kg for wheat straw and 0.23 to 0.087 mg eq/kg for wheat grain (only PBI 120 and 365 d).

Parent pendimethalin was identified in most matrices, however mainly as a minor compound: 1.2–19% TRR in lettuce (0.001–0.02 mg eq/kg), 1.0–2.3% TRR in radish roots and tops (0.001 mg eq/kg), 0.7% TRR in wheat forage (0.002 mg eq/kg), 1.1–4.7% TRR in wheat hay (0.006–0.11 mg eq/kg) and 0.4% TRR (0.001 mg eq/kg) in wheat grain. The only metabolite identified was M455H030, exclusively found in radish roots from the 30 day PBI, amounting 0.011 mg eq/kg (13% TRR).

Most of the extracted radioactivity was characterised as polar, while hydrolysis of the residual radioactivity indicated incorporation into starch (grain) and cellulose (all other matrices).

In the second study ^{14}C-4-methyl-pendimethalin was applied to bare soil with an application rate equivalent to 2.2 kg ai/ha. Plant-back intervals of 30, 90, 110, 270 or 365 days were used, depending on the crop. Rotational crops investigated were lettuce, snap beans, carrots and wheat.

In lettuce, TRR levels were 0.24 mg eq/kg for the 30 d PBI, 0.06–0.37 mg eq/kg for the 90 day PBI and 0.03–0.12 mg eq/kg for the 365 day PBI. Parent pendimethalin (0.021 mg eq/kg, 9.1% TRR) and traces of M455H025 (0.003 mg eq/kg, 1.3% TRR) were only identified in samples from the shortest PBI.

For snap beans the results were comparable to lettuce. In plants TRR levels were 0.07–0.52 mg eq/kg for the 30 d PBI, 0.16 mg eq/kg for the 90 d PBI and 0.07–0.14 mg eq/kg for the 365 day PBI. In the beans TRR levels were lower, amounting 0.07 mg eq/kg, 0.02 mg eq/kg and 0.06 mg eq/kg, respectively. Again, pendimethalin (0.012 mg eq/kg, 2.3% TRR) and traces of M455H025

(0.006 mg eq/kg, 1.2% TRR) were found in whole plant samples from the shortest PBI, but not in samples collected later. Bean samples were not subject to identification.

In root crops residues in roots were significantly higher than in greens. For the greens, TRR levels declined from 0.2 mg eq/kg (30 d PBI), over 0.09–0.15 mg eq/kg (90 d PBI) to 0.02–0.08 mg eq/kg (365 day PBI). In roots, corresponding residues for the PBIs were 0.29 mg eq/kg, 0.15–0.59 mg eq/kg and 0.04–0.19 mg eq/kg, respectively. In roots, substantial residues of pendimethalin were found, amounting to 0.13 mg eq/kg (46% TRR) for the 30 day PBI and 0.07 mg eq/kg (51% TRR) for the 90 day PBI. In addition traces of M455H025 were found, but its levels did not exceed 0.01 mg eq/kg.

In wheat matrices TRR levels were comparably low, with straw showing highest residues of 0.15–0.19 mg eq/kg in all PBIs investigated. Grain showed much lower total radioactive residues amounting 0.01–0.03 mg eq/kg. Only straw was analysed for the composition of the radioactivity, however neither pendimethalin nor any metabolites could be identified.

In the third study on confined rotational crops bare soil in the field was treated with 2.1 kg ai/ha of ^{14}C-phenyl-pendimethalin. Directly after treatment soya beans were planted on all plots. After harvest of the soya beans (89 DAT), the plots were divided into sub-plots and wheat, lettuce and radish (at 90 DAT) and lettuce and radish (at 270 DAT) were planted as rotational crops.

The TRR levels of crops planted after 90 or 270 days were relatively similar, ranging from 0.007 to 0.095 mg eq/kg. The majority of the radioactivity could be extracted (51–95% TRR), except for wheat grain (33% TRR).

Identification of the radioactivity indicated pendimethalin in all samples. In lettuce and radish roots+tops pendimethalin was present at major amounts, representing < 5% up to 33% of the TRR (< 0.003 to 0.025 mg eq/kg). In wheat matrices pendimethalin was identified, however below the LOQ (< 0.003 mg eq/kg, < 5% TRR). Besides pendimethalin, M455H025 was indentified in nearly all matrices. However, it did not exceed 7% TRR (0.004 mg eq/kg).

In summary residues of pendimethalin are taken up via roots and treated plant parts and transported into aerial parts. Within the plants, the active substance is quickly and almost completely metabolized into numerous minor metabolites before the radioactivity is finally incorporated into natural products.

In primary treated plants following pre-emergence or early post-emergence treatment significant metabolites were abundant. In rotational crops, especially root crops, parent pendimethalin was the major residue often being present in amounts exceeding 10% TRR and 0.01 mg eq/kg. M455H025 was also identified in most matrices obtained from confined rotational crop studies, however its concentrations did not exceed 10% TRR and 0.01 mg eq/kg. In one confined rotational crop study, M455H030 was found as a major metabolite exclusively in radish roots (0.011 mg eq/kg, 13% TRR).

Animal metabolism

Information was available on the metabolism of pendimethalin in laboratory animals, lactating goats and laying hens.

For lactating goats four studies were conducted involving daily administration of either ^{14}C-phenyl- or ^{14}C-4-methyl-pendimethalin.

In the first study ^{14}C-4-methyl-pendimethalin was administered to four lactating goats at 0.5, 1.5 or 20 ppm in the diet for ten consecutive days. Most of the administered radioactivity was recovered from faeces (54–67% AR) and urine (9.7–15% AR). In the lowest dose group only liver and kidney contained quantifiable radioactive residues of 0.03 and 0.01 mg eq/kg, respectively. In the second dose group, again liver and kidney gave the highest TRR levels of 0.04 mg eq/kg each. In fat TRR at the LOQ of 0.01 mg eq/kg was detected. In the highest dose group, liver gave the highest

TRR with 0.25 mg eq/kg, followed by kidney (0.09 mg eq/kg), fat (0.03 mg eq/kg) and milk (0.01 mg eq/kg). In muscle no residue above the LOQ were found for any of the dose-groups. Identification of specific compounds in the TRR was not achieved, due to the virtual complete metabolism of the parent compound.

In a second study two lactating goats were administered ^{14}C-phenyl-pendimethalin at rates of 2.1 or 6.3 ppm in the diet for seven consecutive days. TRR levels found did not exceed the LOQs (edible tissues: < 0.05 mg eq/kg and milk: < 0.01 mg eq/kg) except for liver, which contained 0.05 mg eq/kg after administration of 2.1 ppm and 0.17 mg eq/kg after administration of 6.3 ppm. No identification of the radioactivity was performed.

The third study involved administration of ^{14}C-phenyl-pendimethalin to two goats at rates of 6.5 ppm in the diet for seven consecutive days. The excretion of the radioactivity was primarily via faeces (65–68% AR), followed by urine (11–15% AR). Liver was the only tissue analysed for residues, containing TRR levels of 0.077 to 0.096 mg eq/kg. The identification of the liver extracts showed a broad distribution of the radioactivity over the whole retention time of the chromatogram with no analytical peak exceeding 7% of the TRR (0.005 mg eq/kg). No metabolite structures could be attributed to the findings.

In the fourth study one lactating goat received ^{14}C-phenyl-pendimethalin at a dose equivalent to 15.4 ppm in the diet (0.75 mg/kg bw) for five consecutive days. The administered dose was mainly recovered in the faeces (67%), followed by urine (15%) and the GI tract (12%). In edible matrices highest TRR levels were found in liver (0.32 mg eq/kg), while other matrices contained 0.042 mg eq/kg in kidney, 0.0082 mg eq/kg in fat, up to 0.0076 mg eq/kg in milk and 0.0022 mg eq/kg in muscle. Solvent extraction using methanol:water released 64% TRR from liver and 81% from kidneys. Identification of the radioactivity was performed for kidney and liver including pepsin treatment of the extracts. In kidney, numerous minor metabolites were present at individual concentrations insufficient for identification (< 0.005 mg eq/kg). In liver, also many metabolites were observed. Pendimethalin was detected in traces below the LOQ. The only major metabolite in goat liver exceeding either 10% TRR or 0.05 mg eq/kg was M455H029 (14% TRR, 0.043 mg eq/kg).

For laying hens the metabolism of pendimethalin was investigated by administration of ^{14}C-phenyl-labelled pendimethalin for 5 consecutive days at doses of 0.5 or 10 ppm in the diet (5 or 10 animals per dose group). Animals were sacrificed approximately 22 hours after the last dosing. Analysis of daily composites of excreta showed average recoveries of 85% and 88% AR in the low and high treatment, respectively.

TRR levels for tissue and eggs were below 0.01 mg eq/kg for the 0.5 ppm group. In the high dose group (10 ppm) TRR levels in eggs ranged from < 0.01 to 0.035 mg eq/kg. A plateau of radioactivity in eggs was not reached within the seven day dosing period. Muscle residues following administration of 10 ppm were also below 0.01 mg eq/kg. TRR levels found in tissues were < 0.01 mg eq/kg in muscle, 0.2 mg eq/kg in liver and 0.035 mg eq/kg in skin with adhering fat.

In the attempt to identify the radioactive residues present in tissues and eggs, no substances present at or above the LOQ (0.01 mg eq/kg) were found. In eggs and liver traces of parent pendimethalin were found, however at levels too low for quantification.

In summary the metabolic degradation of pendimethalin in livestock animals was significant and often complete. In laying hens tissues and eggs as well as in goats milk and all tissues except liver no metabolites were identified since individual concentration were below detection limits. In goat liver M455H029 was the only metabolite exceeding 10% TRR or 0.05 mg eq/kg. Radioactive residues were highest in liver, followed by kidney, fat, milk/eggs and muscle.

Environmental fate in soil and air

The Meeting received information for pendimethalin on soil and aqueous photolysis, aqueous hydrolysis and aerobic soil metabolism.

Soil photolysis using ^{14}C-phenyl-pendimethalin indicated low degradation within 15 days continuous irradiation (76% AR remaining). Following the assumption of 1st order kinetics, a half-life of approximately 46 days was estimated.

Aqueous photolysis was investigated in sterile buffer solutions adjusted to a pH of 7. ^{14}C-phenyl-pendimethalin in irradiated samples was degraded, leaving only 4.8% of the parent substance at the end of the experiment after 15 days of continuous irradiation. The half-life was estimated between 3–7 days. In control samples kept in the dark no degradation of pendimethalin was observed.

Hydrolysis in aqueous solutions representative to extreme environmental conditions (50 °C) showed no degradation at pH 5, 7 and 9 within 5 days. It can be assumed that pendimethalin is hydrolytical stable under environmental conditions.

In the aerobic soil metabolism studies ^{14}C-phenyl-pendimethalin was moderately persistent with half-life of 64–225 days in microbial active soil (geom. mean: 102 days). The only metabolite identified was M455H001, present at a maximum of 7.0% of the TRR at the end of the study. Unextracted residues in soil at the end of the studies were 36% of the AR. Mineralisation into CO_2 was low with < 10% AR.

Due to the relatively high vapor pressure of 1.39×10^{-3} Pa, pendimethalin is susceptible to volatilisation and evaporation from treated crops (up to 13% within the first 5 days after treatment). EC or SC formulations showed significantly higher volatilization than CS formulations.

In field rotational crop studies bare soil was treated with rates equivalent to 4.5–4.6 kg ai/ha. Wheat was grown as primary crop after different intervals and removed from the field 4, 9 or 12 months after the soil treatment. In wheat, radish or lettuce matrices grown as succeeding crops, no residues of pendimethalin above the LOQ of 0.05 mg/kg were found.

The highest annual application rates for rotated crops are reported from the USA with 6.7 kg ai/ha and season, however a general label restriction was implemented to avoid crop rotation with crops not covered by US registrations within 24 months (or 12 months when < 1.9 kg ai/ha were applied). The Meeting concluded that this interval is sufficient to avoid residues above the LOQ in rotational crops.

In summary the Meeting concluded that pendimethalin is moderately persistent in soil under laboratory conditions. The geometric mean of DT_{50} values was 102 days, suggesting a low potential for accumulation in soil.

Soil photolysis is a minor pathway of degradation in the environment whereas photolytical degradation in water is relatively fast. However, pendimethalin was stable under hydrolytic conditions.

The transfer of pendimethalin into rotated crops is limited and application of established label restrictions and the results of the field rotational crop study, no significant residues (≥ 0.01 mg/kg) are to be expected in plant commodities obtained from rotational crops.

Methods of analysis

The Meeting received analytical methods for pendimethalin, M455H025 and M455H029 in plant and animal matrices. The basic principle employs liquid extraction by homogenisation with methanol/water, matrix depended with addition of methylene chloride, acetone or ethyl acetate/cyclohexane. Clean-up is normally achieved by C18 solid-phase extraction or gel permeation chromatography. Residues are determined by LC-MS/MS, GC-NPD or GC-MS.

The methods submitted are suitable for measuring pendimethalin and M455H025 with a LOQ of 0.01 mg/kg in all plant matrices,

In animal matrices, pendimethalin can be measured in tissues, milk and eggs with a LOQ of 0.01 mg/kg by GC-MS. LC-MS/MS methods were validated for pendimethalin, M455H025 and

M455H029 with LOQs of 0.01 mg/kg in milk and of 0.05 mg/kg and animal tissues. For M455H025 and M455H029 no analytical methods for their determination in eggs were provided.

The application of multi-residue methods was tested with QuEChERS and DFG S19 for plant and animal matrices. The methods weresuitable with a general LOQ of 0.01 mg/kg for parent pendimethalin.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the storage stability of pendimethalin and M455H025 in plant matrices stored at -18 °C.

In plant matrices with high water, high starch and high acid content pendimethalin and M455H025 were stable for at least 24 months. Soya bean and almond nutmeat, which are representative commodities for high oil content matrices, were stable for up to 18 and 12 months, respectively.

Residues were stable in milk, cream and fat for up to 2 months for pendimethalin and for at least 3 months for M455H025 and M455H029.

Definition of the residue

The fate of pendimethalin in plants was investigated after pre-emergence or early post-emergence treatment to onions, sweet corn, lettuce, carrots, potatoes and wheat. In all crop samples investigated pendimethalin was significantly degraded into numerous minor metabolites. In addition incorporation of radioactivity into cellulose and soluble carbohydrates was observed. Although mainly present at minor amounts in all matrices, parent pendimethalin was the dominant residue and often the only compound identified (0.8% TRR in wheat grain up to 16% TRR in carrot roots). In whole plants of sweet corn and in carrots leaves the metabolites CL217146 and M455H025 were found at low proportions (up to 4.6% TRR), but not in grain or the roots. In wheat feed matrices (hay, straw and chaff) the isomeric mixtures M455H002-M455H003, M455H005- M455H008 and M455H009-M455H010 were identified, but also in minor amounts not exceeding 3.4% TRR. Other matrices did not contain identified metabolites.

In confined rotational crop studies uptake of radioactivity into plants was observed. Pendimethalin was the dominant residue often being present in major amounts exceeding 10% TRR, especially in root crops. M455H025 was also identified in most matrices, however at lower proportions than parent pendimethalin, not exceeding 7% TRR (0.004 mg eq/kg). In one confined rotational crop study, M455H030 was found as a major metabolite exclusively in radish roots (0.011 mg eq/kg, 13% TRR). Again, in all crops a large part of the radioactivity was incorporated into natural products like cellulose and carbohydrates.

In supervised field trials, when M455H025 was found in concentrations above the LOQ, residues of pendimethalin were normally at least one order of magnitude higher.

The Meeting concluded that pendimethalin is the major residue in primary treated plants and in rotational crops and is suitable for compliance with MRLs. Analytical multi-residue methods are capable of measuring pendimethalin in all plant matrices.

For dietary risk assessment, pendimethalin was the predominant residue found in plant metabolism studies and in supervised field trials and has to be considered for intake purposes for plant commodities. M455H025 and M455H030 were identified as possibly significant plant metabolites. Both compounds are unlikely to be genotoxic, but are not covered by the toxicological reference values for pendimethalin.

M455H025 was identified in plant and rotational crop metabolism studies, but was not found in quantifiable levels in harvested food commodities under field conditions. Its estimated exposure is

up to 1.3 µg/kg bw, assuming M455H025 to be present at concentrations of 0.05 mg/kg (LOQ used in field rotational crop studies) in all food commodities obtained from annual crops.

M455H030 was found as a major metabolite exclusively in rotated radish roots, but not in any other crop. The expected exposure of M455H030 is up to 0.1 µg/kg bw.

The Meeting concluded, that the exposure of both M455H025 and M455H030 is below the TTC for a Cramer Class III compound (1.5 µg/kg bw) and is therefore unlikely to present a public health concern based on the uses considered by the Meeting.

In summary, the Meeting concluded that parent pendimethalin is the relevant residue in all plant matrices for dietary intake purposes.

Livestock animal metabolism studies were conducted on lactating goats (0.5–20 ppm in the diet) and laying hens (0.5–10 ppm).

Parent pendimethalin was not found in milk and tissues of lactating goats. In a feeding studies on dairy cattle at 760 ppm, fat, whole milk and cream contained residues of the parent up to 0.1 mg/kg. Metabolism studies showed that M455H029 was the only major metabolite found in ruminants, being present at 14% TRR (0.043 mg eq/kg) in liver exclusively. The feeding study indicated residues if this metabolite at concentrations up to 1.0 mg/kg in liver and 0.49 mg/kg in kidney. M455H025 was not detected in tissues and milk in goat metabolism studies. However, in the feeding study one positive finding in milk was reported containing 0.012 mg/kg.

Tissues and eggs from laying hens did not contain radioactive residues at individual concentrations sufficient for identification. In eggs, traces of pendimethalin were detected, but also at levels below the LOQ. A feeding study on poultry was not submitted.

The Meeting concluded that pendimethalin is almost completely metabolized in lactating goats and laying hens, primarily in the liver. In bovine fat, milk and cream as well as in eggs the parent substance was present. M455H029 was exclusively present in bovine liver and kidney only, while M455H025 was found at low amount in cream only. For compliance with MRLs the Meeting concluded that pendimethalin is a suitable marker in animal commodities. Analytical multi-residue methods are capable of measuring pendimethalin in all animal matrices.

In all species TRR levels in fatty tissues or egg yolk were higher than in muscle tissues or egg white. In a feeding study on lactating cows using pendimethalin, residues above the LOQ were found in cream and fat but not in skim milk or muscle. However, residue ratios between fatty and non-fatty matrices were not significant. The log P_{ow} of pendimethalin is 5.4. The Meeting concluded that the information available from animal studies is inconclusive concerning the fat-solubility, but decided that residues of pendimethalin are fat soluble taking into account the high log P_{ow} for the compound.

For dietary intake purposes pendimethalin is the primary residue identified in fat, milk, cream and eggs and has to be considered for intake purposes for animal commodities. M455H025 and M455H029 were identified as possibly significant metabolites in animal commodities. The TTC approach presented for M455H025 as a plant metabolite also covers its occurrence in animal matrices, since it is found in minor amounts in cream only contributing insignificantly to the total exposure.

M455H029 is unlikely to be genotoxic, but is not covered by the toxicological reference values for pendimethalin. It was exclusively found in ruminant liver and kidney, resulting in an overall exposure of up to 0.3 µg/kg bw. Since the estimated exposure of M455H029 is below the respective trigger value of the TTC approach for a Cramer Class III compound (1.5 µg/kg bw), it is unlikely to present a public health concern based on the uses considered by the Meeting.

In summary, the Meeting concluded that parent pendimethalin is the relevant residue in all animal matrices for dietary risk assessment.

Definition of the residue for compliance with MRL and for dietary intake for plant and animal commodities: *Pendimethalin*

The residue is fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised trial data for applications of pendimethalin on citrus fruit, bulb vegetables, leaf lettuce, brassica leafy vegetables, legume vegetables, carrots, celeriac, asparagus, celery, tree nuts hops and animal feedstuffs conducted in Europe and the USA.

Citrus fruits

Pendimethalin is registered in the USA for weed control under citrus trees at maximum rates of 1 × 6.7 kg ai/ha with a PHI of 1 day. Supervised field trials from the USA according to this GAP were submitted.

In grapefruit (whole fruits) residues of pendimethalin following GAP treatment were (n = 6): < 0.005(5), 0.0075 mg/kg.

In lemons (whole fruits) residues of pendimethalin following GAP treatment were (n = 4): < 0.005, 0.0055, 0.009, 0.019 mg/kg.

In oranges (whole fruits) residues of pendimethalin following GAP treatment were (n = 9): < 0.005(9) mg/kg.

The Meeting noticed that pendimethalin is registered in the USA for the whole group of citrus fruits and decided to explore the possibility for a group recommendation. The median of the commodities investigated are within a 5-fold range. Statistical testing was not applied to the datasets due to the high number of censored data; however since pendimethalin is applied to the ground beneath trees for weed control, morphological differences between citrus sub-groups are expected to be of low influence on the magnitude of the residue. Therefore the Meeting decided to combine all residue data on citrus to provide a robust basis for the estimation of maximum residue levels.

The combined residues of pendimethalin in citrus fruits following GAP treatment were (n = 19): < 0.005 (15), 0.0055, 0.0075, 0.009 and 0.019 mg/kg.

The Meeting estimated a maximum residue level of 0.03 mg/kg, an STMR value of 0.005 mg/kg and an HR of 0.019 mg/kg in citrus fruits (whole fruits).

Bulb onion and fennel

Pendimethalin is registered in Austria for the use on bulb vegetables and fennel with one post-emergence treatment at 1.6 kg ai/ha. Supervised field trials from Europe on bulb onions and fennel according to this GAP were submitted.

In bulb onions residues of pendimethalin following GAP treatment were (n = 9): < 0.01(5), < 0.05(4) mg/kg.

In fennel bulbs residues of pendimethalin following GAP treatment were (n = 4): < 0.02(4) mg/kg.

In the USA pendimethalin is registered for the use on bulb onions with 2 × 1.1 kg ai/ha (2.1 kg ai/ha season max.) and a PHI of 30 days, on garlic with 2 × 1.7 kg ai/ha and a PHI of 45 days and on shallots with 3 × 2.1 kg ai/ha (6.7 kg ai/ha season max.) and a PHI of 45 days. Supervised field trials on bulb onions from the USA were submitted matching or exceeding (+50%) the maximum total seasonal rate within this group on shallots but with two treatments only instead of three.

In bulb onions residues of pendimethalin following treatment at exaggerated rates were (n = 6): < 0.05(6) mg/kg.

The Meeting noticed that supervised field trials matching the Austrian GAP or the US GAP did not result in residues of pendimethalin above the LOQ, even in trials involving treatment at exaggerated rates in the USA.

The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR and HR of 0 mg/kg for pendimethalin in the bulb onions and decided to extrapolate the estimate to bulb fennel, garlic and shallots also.

Spring onions and Welsh onions

Pendimethalin is registered in the USA for the use on the green onions group at BBCH 13 with 2 × 1.1 kg ai/ha (2.1 kg ai/ha season max.) and a PHI of 30 days. Three supervised field trials on green onions from the USA were submitted matching the GAP.

In green onions residues of pendimethalin following GAP treatment were (n = 3): 0.095, 0.095 and 0.12 mg/kg.

Pendimethalin is also registered in Germany for the use on leek with one post-emergence treatment at 1.6 kg ai/ha. Two supervised field trials from Europe according to this GAP were submitted.

In leek residues of pendimethalin following GAP treatment were (n = 2): < 0.01(2) mg/kg.

Based on the US GAP, the Meeting estimated a maximum residue level of 0.4 mg/kg, an STMR value of 0.095 mg/kg and an HR of 0.12 mg/kg in spring onions and Welsh onions.

Leaf lettuce

In the USA pendimethalin is registered for the use on the lettuce at BBCH 13 with 1 × 1.1 kg ai/ha and a PHI of 20 days. Supervised field trials on leaf lettuce from the USA were submitted matching the GAP.

In leaf lettuce residues of pendimethalin following GAP treatment were (n = 9): < 0.05, < 0.05, 0.058, 0.06, 0.062, 0.094, 0.14, 0.3 and 2.2 mg/kg.

The Meeting estimated a maximum residue level of 4 mg/kg, an STMR of 0.062 mg/kg and an HR of 2.2 mg/kg for pendimethalin in leaf lettuce.

Brassica leafy vegetables

Pendimethalin is registered in the USA for the use on all commodities of the Codex group brassica leafy vegetables. In Germany, a singular GAP is registered on kale, resulting in a higher maximum residue estimate. Therefore the Meeting decided to consider a maximum residue level for the whole group of brassica leafy vegetables, except kale, based on the US GAP and to consider a separate, higher level for kale, based on the German GAP:

Brassica leafy vegetables, except kale

In the USA pendimethalin is registered for the use on the "leafy brassica greens including mustard greens" at BBCH 15 with 1 × 1.1 kg ai/ha and a PHI of 21 days. Supervised field trials on mustard greens from the USA were submitted matching the GAP.

In mustard greens residues of pendimethalin following GAP treatment were (n = 6): < 0.05(4), 0.1 and 0.11 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg, an STMR of 0.05 mg/kg and an HR of 0.11 mg/kg for pendimethalin in brassica leafy vegetables, except kale.

Kale

In Germany pendimethalin is registered for the use on kale with 1 × 1.6 kg ai/ha at BBCH 16 and a PHI of 60 days. Supervised field trials on kale from Europe were submitted matching the GAP.

In kale residues of pendimethalin following GAP treatment were (n = 4): < 0.05(3) and 0.25 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg, an STMR of 0.05 mg/kg and an HR of 0.25 mg/kg for pendimethalin in kale.

Beans, except broad bean and soya bean (green pods and immature seeds)

In Germany pendimethalin is registered for the use on fresh beans with 1 × 2.0 kg ai/ha before emergence of the crops. Supervised field trials on fresh beans from Europe were submitted matching the GAP.

In beans with pods residues of pendimethalin following GAP treatment were (n = 9): < 0.05(9) mg/kg.

The Meeting estimated a maximum residue level of 0.05* mg/kg and a STMR and HR of 0.05 mg/kg for pendimethalin in Beans, except broad bean and soya bean (green pods and immature seeds).

Peas (pods and succulent = immature seeds)

In Greece pendimethalin is registered for the use on fresh peas with 1 × 2.0 kg ai/ha. Supervised field trials on fresh peas from Europe were submitted matching the GAP.

In peas with pods residues of pendimethalin following GAP treatment were (n = 15): < 0.01(13), 0.012, 0.014 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg, an STMR of 0.01 mg/kg and an HR of 0.014 mg/kg for pendimethalin in peas (pods and succulent = immature seeds).

Peas, shelled (succulent seeds)

In Greece pendimethalin is registered for the use on legume fresh peas with 1 × 2.0 kg ai/ha. Supervised field trials on legume fresh peas from Europe were submitted matching the GAP.

In peas without pods residues of pendimethalin following GAP treatment were (n = 15): < 0.01(13), 0.022, 0.036 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg, an STMR of 0.01 mg/kg and an HR of 0.036 mg/kg for pendimethalin in peas, shelled (succulent seeds).

Beans and peas (dry seeds)

In Germany pendimethalin is registered for the use on beans and peas with 1 × 2.0 kg ai/ha pre-emergent to the crops. Supervised field trials on beans from Europe were submitted matching the GAP.

In beans (dry seeds) residues of pendimethalin following GAP treatment were (n = 9): < 0.05(9) mg/kg.

The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg for pendimethalin in beans (dry) and agreed to extrapolate the result to peas (dry).

Carrots

In Czech Republic pendimethalin is registered for the use on carrots with 1 × 1.7 kg ai/ha. Supervised field trials on carrots from Europe were submitted matching the GAP.

In carrot roots residues of pendimethalin following GAP treatment were (n = 16): 0.019, 0.023, 0.031, 0.033, 0.038, 0.046, 0.051, 0.058, 0.067, 0.073, 0.073, 0.084, 0.13, 0.16, 0.27 and 0.38 mg/kg.

In the USA pendimethalin is registered for the use on carrots with 1 × 1.1 kg ai/ha and a PHI of 60 days. No trials matching the GAP were submitted.

Based on the GAP from Czech Republic, the Meeting estimated a maximum residue level of 0.5 mg/kg, an STMR of 0.0625 mg/kg and an HR of 0.38 mg/kg for pendimethalin in carrots.

Celeriac

In the Austria pendimethalin is registered for the use on celeriac with 1 × 1.6 kg ai/ha at BBCH 13 and a PHI of 60 days. Supervised field trials on celeriac from Europe were submitted matching the GAP.

In celeriac residues of pendimethalin following GAP treatment were (n = 3): < 0.02, < 0.02 and 0.061 mg/kg.

The Meeting concluded that the number of supervised field trials submitted for celeriac was insufficient for the estimation of maximum residue levels.

Asparagus

In Greece pendimethalin is registered for use on asparagus with 1 × 2.0 kg ai/ha before emergence of the crop. Supervised field trials on asparagus from Europe were submitted matching the GAP.

In asparagus spears residues of pendimethalin following treatment according to the Greek GAP were (n = 4): < 0.05, < 0.05, 0.05 and 0.06 mg/kg.

In the USA pendimethalin is registered for the use on asparagus with 1 × 4.4 kg ai/ha before emergence of the crop with a PHI of 14 days. Supervised field trials on asparagus from the USA were submitted matching the GAP.

In asparagus spears residues of pendimethalin following treatment according to the US GAP were (n = 4): < 0.05, < 0.05, 0.05 and 0.058 mg/kg. A single highest duplicate sample resulted a residue of 0.062 mg/kg.

Based on the US GAP the Meeting estimated a maximum residue level of 0.1 mg/kg, an STMR of 0.05 mg/kg and an HR of 0.062 mg/kg for pendimethalin in asparagus.

Celery

Pendimethalin is registered in Austria for the use on celery with one treatment of 1.6 kg ai/ha at BBCH 13 and a PHI of 60 days. Supervised field trials from Europe according to this GAP were submitted.

In celery residues of pendimethalin following GAP treatment were (n = 8): < 0.01(2), < 0.02(3), 0.02, 0.045 and < 0.05 mg/kg.

The Meeting estimated a maximum residue level of 0.09 mg/kg, an STMR of 0.02 mg/kg and an HR of 0.05 mg/kg for pendimethalin in celery.

Rhubarb

In the Germany pendimethalin is registered for the use on rhubarb with 1 × 1.6 kg ai/ha before emergence. Supervised field trials on rhubarb from Europe were submitted matching the GAP.

In rhubarb residues of pendimethalin following GAP treatment were (n = 2): < 0.02 and < 0.02 mg/kg.

The Meeting concluded that the number of supervised field trials submitted for rhubarb is insufficient for the estimation of maximum residue levels.

Tree nuts

In the USA pendimethalin is registered for the control of ground weeds on tree nuts with 1 × 6.7 kg ai/ha with a PHI of 60 days. Supervised field trials on almonds, pecan, pistachios and walnuts from the USA were submitted matching the GAP.

In almond nutmeat residues of pendimethalin following according to GAP were (n = 7): < 0.05(7) mg/kg.

In pecan nutmeat residues of pendimethalin following according to GAP were (n = 7): < 0.05(7) mg/kg.

In pistachio nutmeat residues of pendimethalin following according to GAP were (n = 2): < 0.05 and < 0.05 mg/kg.

In walnuts nutmeat residues of pendimethalin following according to GAP were (n = 1): < 0.05 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR and an HR of 0.05 mg/kg for pendimethalin in tree nuts.

Hops, dry

In the USA pendimethalin is registered for the control of ground weeds on hops with 1 × 4.5 kg ai/ha with a PHI of 90 days. Supervised field trials on hops from the USA were submitted matching the GAP.

In hops, dried cones, residues of pendimethalin following according to GAP were (n = 4): < 0.<u>05</u>(4) mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.05 mg/kg for pendimethalin in hops, dry.

Alfalfa forage (green)

In the USA pendimethalin is registered for the use on alfalfa (until 15cm height) with up to 4.5 kg ai/ha. The PHI differs depending on the amount applied: if ≤ 1.9 kg ai/ha are applied the PHI is 28 days, if more is applied the PHI is 50 days. Supervised field trials on alfalfa forage from the USA were submitted matching the GAP.

After treatment of the maximum rate of 4.5 kg ai/ha and a PHI of 50 days, residues of pendimethalin in alfalfa forage were (n = 5): < 0.05, < 0.05, 0.24, 0.25, 1.2 mg/kg.

After treatment of up to 1.9 kg ai/ha and a PHI of 28 days, residues of pendimethalin in alfalfa forage were (n = 9): < 0.05, 0.08, 0.1, 0.12, <u>0.12</u>, 0.13, 0.31, 0.57, 2.7 mg/kg.

Based on the critical GAP involving application of up to 1.9 kg ai/ha and a PHI of 28 days the Meeting estimated a median residue of 0.12 mg/kg and a highest residue of 2.7 mg/kg for pendimethalin in alfalfa forage.

Bean forage (green)

In Germany pendimethalin is registered for the use on fresh beans with 1 × 2.0 kg ai/ha before emergence of the crops. Supervised field trials on fresh beans from Europe were submitted matching the GAP.

In bean forage residues of pendimethalin following GAP treatment were (n = 9): < 0.05(5), 0.07, 0.17, 0.18 and 0.33 mg/kg.

The Meeting estimated a median residue of 0.05 mg/kg and a highest residue of 0.33 mg/kg for pendimethalin in bean vines, fresh.

Grass forage

In the USA pendimethalin is registered for the use on grassland with up to 4.5 kg ai/ha. No grazing or pre-harvest interval was established. Supervised field trials on grassland from the USA were submitted matching the GAP.

The Meeting noted that residues of pendimethalin in grass decline quickly, resulting in substantially lower residues within the first days after harvest. Forage grasses are continuously grazed/fed, therefore the singular high residue data in forage collected directly after treatment (day 0) is expected to result in an unrealistic estimate of the livestock animal dietary burden in relation to the 28 day feeding studies available. The Meeting decided to use residue data after 15 days in grass forage to provide a more realistic estimate.

In grass forage residues of pendimethalin after 15 days following GAP treatment were (n = 12): 2.8, 12, 16, 19, 30, 34, 38, 42, 43, 48, 64 and 199 mg/kg.

The Meeting estimated a median residue of 36 mg/kg and a highest residue of 199 mg/kg for pendimethalin in grass forage (as received).

Alfalfa fodder

In the USA pendimethalin is registered for the use on alfalfa (until 15cm height) with up to 4.5 kg ai/ha. The PHI differs depending on the amount applied: if ≤ 1.9 kg ai/ha are applied the PHI is 28 days, if more is applied 50 days. Supervised field trials on alfalfa forage from the USA were submitted matching the GAP.

After treatment of the maximum rate of 4.5 kg ai/ha and a PHI of 50 days, residues of pendimethalin in alfalfa forage were (n = 5): 0.13, 0.57, 0.97, 1.1, 2.1 mg/kg.

After treatment of up to 1.9 kg ai/ha and a PHI of 28 days, residues of pendimethalin in alfalfa forage were (n = 9): 0.07, 0.08, 0.21, 0.35, 0.54, 0.78, 0.83, 0.85, 1.6 mg/kg.

Based on the critical GAP involving application of up to 4.5 kg ai/ha and a PHI of 50 days the Meeting estimated a median residue of 0.97 mg/kg and a highest residue of 2.1 mg/kg for pendimethalin in alfalfa fodder (as received).

Based on an average dry-matter content of 89% the Meeting estimated a maximum residue level of 4 mg/kg for alfalfa fodder (dry weight basis).

Bean fodder

In Germany pendimethalin is registered for the use on beans with 1 × 2.0 kg ai/ha before emergence of the crops. Supervised field trials on bean straw and fodder from Europe were submitted matching the GAP.

In bean straw residues of pendimethalin following GAP treatment were (n = 9): < 0.05(8), 0.11 mg/kg.

The Meeting estimated a median residue of 0.05 mg/kg and a highest residue of 0.11 mg/kg for pendimethalin in bean fodder (as received).

Based on an average dry-matter content of 88% (http://www.feedipedia.org/node/12006) the Meeting estimated a maximum residue level of 0.3 mg/kg (dry weight basis).

Hay or fodder (dry) of grasses

In the USA pendimethalin is registered for the use on grassland with up to 4.5 kg ai/ha without grazing or pre-harvest interval. Supervised field trials on grassland from the USA were submitted matching the GAP.

In grass hay residues of pendimethalin following GAP treatment were (n = 12): 23, 100, 259, 286, 364, 404, 581, 590, 640, 794, 930, 1030 mg/kg.

The Meeting estimated a median residue of 492.5 mg/kg and a highest residue of 1030 mg/kg for pendimethalin in grass hay (as received).

Based on an average dry-matter content of 88%, the Meeting estimated a maximum residue level of 2500 mg/kg (dry weight basis) for hay or fodder (dry) of grasses.

Almond hulls

In the USA pendimethalin is registered for the control of ground weeds on almonds with 1 × 6.7 kg ai/ha with a PHI of 60 days. Supervised field trials on almond hulls from the USA were submitted matching the GAP.

In almond hulls residues of pendimethalin following according to GAP were (n = 6): 0.19, 0.22, 0.28, 0.56, 2.0, 2.6 mg/kg.

The Meeting estimated a median residue of 0.42 mg/kg for pendimethalin in almond hulls (as received).

Based on an average dry-matter content of 90% the Meeting estimated a maximum residue level of 7 mg/kg (dry weight basis).

Fate of residues during processing

The Meeting received information on the hydrolysis of ^{14}C-phenyl-pendimethalin as well as processing studies on grapefruit, oranges, carrots and alfalfa.

In a hydrolysis study using ^{14}C-phenyl-pendimethalin typical processing conditions were simulated (pH 4,5 and 6 with 90 °C, 100 °C and 120 °C for 20, 60 and 20 minutes). No degradation of the parent was observed.

The fate of pendimethalin residues has been examined simulating household and commercial processing of grapefruit, oranges, carrots and alfalfa.

For grapefruit and oranges processing factors could not be derived since residues in raw agricultural commodities were below the LOQ. Data on oranges were suitable for the estimation of a peel-pulp ratio.

Estimated processing factors for the commodities considered at this Meeting are summarised below.

Raw commodity	Processed commodity	Pendimethalin			
		Individual processing factors	Median	STMR-P in mg/kg	HR-P in mg/kg
Oranges (STMR: 0.005 mg/kg, HR: 0.019 mg/kg	Peel	1.4, 2.1, 2.7, 2.8, 2.9, 2.9, 3.6	2.8	0.014	0.053
	Pulp	0.07, 0.09, 0.1, 0.14, 0.16, 0.18, 0.32	0.14	0.0007	0.003
Carrots (STMR: 0.0625 mg/kg, HR: 0.38 mg/kg)	Cooked	< 0.03, < 0.05, < 0.06	< 0.05	< 0.0031	0.019
	Juice	0.38, 0.38, 0.45	0.38	0.024	-
	Pomace, wet	0.66, 0.74, 1.1	0.74	0.046	-
	Canned	< 0.03, < 0.05, < 0.06	< 0.05	< 0.0031	0.019

Residues in animal commodities

Farm animal feeding studies

The Meeting received two feeding studies involving pendimethalin on lactating cows. No poultry feeding study was submitted.

In the first study lactating cows received dosed daily at a level of 760 ppm in the diet for 29 consecutive days. Milk was collected throughout the whole study and tissues were collected after the last administration within 24 hrs after the last dose.

In milk residues of pendimethalin were 0.011 mg/kg. Skim milk and cream were analysed individually, showing residues of < 0.01 mg/kg for skim milk and of 0.023 mg/kg for cream. Muscle, liver and kidney did not contain residues of pendimethalin at or above the LOQ of 0.05 mg/kg. Only in fat tissues mean and maximum concentration of 0.1 mg/kg and 0.18 mg/kg were found, respectively.

Residues of M455H025 were below the LOQ (0.01 mg/kg for milk and 0.05 for tissues) in all samples except one cream sample (0.012 mg/kg). M455H029 was found in liver and kidney at mean/maximum concentration of 0.49/1.2 mg/kg and 1.0/2.5 mg/kg, respectively.

In the second feeding study on lactating cows the animals received daily dosed of 10.4, 29 or 99 ppm for 29 consecutive days. No detectable residues of pendimethalin or its metabolites M455H025 and M455H029 were found in any of the samples (LOQ milk: 0.01 mg/kg, LOQ tissues: 0.05 mg/kg).

For laying hens the metabolism study involved administration of ^{14}C-phenyl-labelled pendimethalin for 5 consecutive days at doses of 0.5 or 10 ppm. No residues present at or above the LOQ (0.01 mg eq/kg) were found. In eggs and liver traces of parent pendimethalin were found, however at levels too low for quantification.

Estimated maximum and mean dietary burdens of livestock and animal commodities maximum residue levels

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are presented in Annex 6. The calculations were made according to the livestock diets from US-Canada, EU, Australia and Japan in the OECD Table (Annex 6 of the 2006 JMPR Report). For the EU dietary burden, it was noted that grass fodder contributed primarily to the intake of layer hens. The Meeting also noted, that in the latest version of the OECD feed table, grass forage and fodder are no longer considered a

relevant feed item for poultry in the EU and therefore decided to delete these commodities from the estimate.

In the USA the use of pendimethalin on grassland is registered with no PHI. Residues of pendimethalin in grass forage are only applied to the US-Canada livestock dietary burden since it is not considered a traded commodity whereas residues in grass hay and fodder are assumed to be traded globally. The Meeting was informed by an official communication of the government of Australia that no fodder crops are imported. Therefore residues of grass hay and fodder are only attributed to the EU and Japanese livestock dietary burden.

	Livestock dietary burden, pendimethalin, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	max.	mean	max.	mean	max.	mean	max.	mean
Beef cattle	74	9.2	590	280	0.78	0.17	470	220
Dairy cattle	360	65	700	340	1.0	0.25	820 [A]	390 [B]
Poultry - broiler	0.01	0.01	0.33	0.06	0.04	0.04	none	none
Poultry - layer	0.01	0.01	0.41 [C]	0.08 [D]	0.04	0.04	none	none

[A] Highest maximum beef or dairy cattle burden suitable for MRL estimates for mammalian meat and milk

[B] Highest mean beef or dairy cattle burden suitable for STMR estimates for mammalian meat and milk

[C] Highest maximum broiler or laying hen burden suitable for MRL estimates for poultry products and eggs

[D] Highest mean broiler or laying hen burden suitable for STMR estimates for poultry products and eggs

none no relevant feed items

Animal commodities maximum residue levels

For beef and dairy cattle a maximum and mean dietary burden of 820 ppm and 390 ppm were estimated, respectively, based on dairy cattle. The estimated dietary burdens are evaluated against a lactating cow feeding study involving administration of pendimethalin at 760 ppm.

Pendimethalin feeding study	Feed level (ppm)	Total residue (mg/kg) in milk	(mg/kg) in muscle	(mg/kg) in kidney	(mg/kg) in liver	(mg/kg) in fat
Maximum residue level: dairy cattle						
Feeding study (HR for each dose group, except for milk)	760	0.011 (cream: 0.23)	< 0.05	< 0.05	< 0.05	0.18
Dietary burden and residue estimate	820	0.012 (cream: 0.25)	< 0.05	< 0.05	< 0.05	0.19
STMR dairy cattle						
Feeding study (Mean for each dose group)	760	0.011 (cream: 0.23)	< 0.05	< 0.05	< 0.05	0.1
Dietary burden and residue estimate	390	0.006 (cream: 0.12)	0.026	0.026	0.026	0.051

The Meeting estimated STMR and HR values of 0.026 mg/kg and 0.05 mg/kg for muscle and edible offal (based on liver and kidney). For fat, STMR and HR values of 0.051 mg/kg and 0.19 mg/kg were estimated, respectively. Corresponding maximum residue levels were estimated at 0.05 mg/kg for edible offal, mammalian (based on liver and kidney) and 0.2 mg/kg for meat (based on the fat) and mammalian fat.

For milk, an STMR value and a maximum residue level of 0.006 mg/kg and 0.02 mg/kg were estimated, respectively. Based on the data for cream and a correction factor of 2.5 for cream to milk fat (40% fat content in cream), the Meeting also estimated an STMR value and a maximum residue level of 0.3 mg/kg and 0.8 mg/kg for pendimethalin in milk fat, respectively.

For poultry a maximum and mean dietary burden of 0.41 and 0.08 ppm were estimated, respectively.

In the farm animal metabolism study on laying hens conducted at 10 ppm, no quantifiable residue above the LOQ of 0.01 mg/kg were found for pendimethalin in any matrix. The Meeting estimated maximum residue levels of 0.01* mg/kg for eggs, poultry meat, poultry fat and poultry, edible offal. The Meeting also estimated STMR and HR values of 0 for these commodities.

RECOMMENDATIONS

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

The Meeting estimated the STMR and MRL values shown below.

Definition of the residue for compliance with MRL and for dietary intake purposes for plant and animal commodities: *Pendimethalin*

The residue is fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The International Estimated Daily Intakes (IEDI) for pendimethalin was calculated from recommendations for STMRs for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 3.

The IEDI of the 17 GEMS/Food cluster diets, based on the estimated STMRs represented 0.1% of the maximum ADI of 0.1 mg/kg bw. The Meeting concluded that the long-term exposure to residues of pendimethalin from uses considered by the Meeting is unlikely to present a public health concern.

Short-term dietary exposure

The International Estimated Short term Intake (IESTI) for pendimethalin was calculated for all food commodities (and their processed fractions) for which maximum residue levels were estimated and for which consumption data were available. The results are shown in Annex 4.

For pendimethalin the IESTI represented 0–4% of the ARfD (1 mg/kg bw) for the general population and 0–10% of the ARfD for children. On the basis of information provided the Meeting concluded that the short-term dietary exposure to residues of pendimethalin, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.