5.17 MANDIPROPAMID (231)

TOXICOLOGY

Mandipropamid is the ISO approved name for 4-chloro-*N*-[2-[3-methoxy-4-(2-propynyloxy)phenyl]ethyl]-α-(2-propynyloxy)-benzeneacetamide (CAS No. 374726-62-2). It is a new fungicide that belongs to the subset mandelamides in the class carboxylic acid amides. The proposed fungicidal mode of action is by inhibition of phospholipid biosynthesis. Mandipropamid has not been evaluated previously by the JMPR and was reviewed by the present Meeting at the request of CCPR. All the pivotal studies contained certificates of compliance with GLP.

Biochemical aspects

The extent of absorption of radiolabelled mandipropamid was similar in male and female rats dosed by gavage. Absorption was incomplete, with 67–74% of the administered dose being absorbed at the lower dose (3 mg/kg bw) and only 30–45% absorbed at the higher dose (300 mg/kg bw). Absorption was more rapid in females, with peak blood concentrations occurring at 4.5 h for the lower dose and 10 h at the higher dose, while for males the values were 8.5 h and 24 h, respectively. Little or no radioactivity was recovered in the expired air (less than 0.16% of the administered dose). Excretion was predominantly via the bile (lower dose) and faeces and > 90% of the administered dose was eliminated within 168 h. In males, a greater proportion of the administered dose was excreted in the faeces, while in females a significantly greater proportion was excreted via the urine. The greater extent of biliary elimination in males than in females was consistent with faecal excretion being the major route of elimination in males (73%) and of lesser importance in females (55%) at the lower dose. Some reabsorption of biliary metabolites was apparent at both doses. Tissue retention of the radiolabelled material was low, even after multiple doses. The total concentration of tissue residues including the carcass was < 0.3%, therefore demonstrating no evidence of bioaccumulation. The highest concentration of residues was found in the liver.

The biotransformation of mandipropamid was relatively simple since no cleavage of the molecule was observed. The major metabolic transformations involved loss of one or both of the propargyl groups of the molecule, followed by glucuronidation and *O*-demethylation, to produce six major metabolites. While the qualitative metabolite profile was largely independent of sex and dose, quantitative differences were found. Increasing the dose resulted in increasing amounts of radioactivity isolated as parent, indicating saturation of metabolic processes.

Toxicological data

Mandipropamid was of low acute toxicity in rats given a single dose orally (LD_{50} > 5000 mg/kg bw), dermally (LD_{50} > 5000 mg/kg bw) or by inhalation (LC_{50} > 5.19 mg/L). Mandipropamid was minimally irritating to the skin and eyes and was not found to be a dermal sensitizer (local lymph node assay in mice).

In short-term studies of toxicity with mandipropamid, the target organ was the liver, at doses that also resulted in decreased body weight and body-weight gain.

In a 90-day dietary study in rats, decreased body weight, body-weight gain and food consumption were observed at doses of 3000 ppm (260 mg/kg bw per day) and above. Various erythrocyte parameters (haemoglobin, erythrocyte volume fraction, mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration) were decreased in both sexes at doses of 3000 ppm (260 mg/kg bw per day) and above. Increases in liver weight (both sexes), plasma gamma-glutamyl transferase (58–105% in females only) at doses of 3000 ppm (260 mg/kg bw per day) and above were not considered to be adverse in the absence of findings of liver toxicity. The periportal hypertrophy/eosinophilia observed in the liver was considered to be treatment-related, but of

questionable toxicological significance given the minimal to slight severity and the lack of any evidence of progression in the long-term study. The NOAEL for short-term toxicity in rats was 500 ppm (41 mg/kg bw per day).

In dogs given capsules containing mandipropamid, increases in liver weights, cholesterol concentration, ALP and ALT activity were seen after 13 weeks at 100 mg/kg bw per day. The NOAEL in the 90-day study in dogs was 25 mg/kg bw per day. In the 1-year study in dogs, body-weight gain and food consumption were decreased at 400 mg/kg bw per day, together with increased liver weight. At 40 mg/kg bw per day or above, there was also increased ALP and ALT activity and minimal to moderate pigmentation of the liver by porphyrin. The NOAEL in the 1-year study in dogs was 5 mg/kg bw per day. Considering the spacing of doses used and on the basis of the similarity of effects observed in the 90-day and 1-year studies in dogs, the overall NOAEL for dogs was 25 mg/kg bw per day.

In a 78-week study, mice were given diets containing mandipropamid at a concentration of 0, 100, 500 or 2000 ppm, equal to 0, 11, 55 or 223 mg/kg bw per day. There were no treatment-related changes in survival, or the incidence of tumours or non-neoplastic lesions. The only significant findings were observed at the highest dose: reductions in body weight and food conversion efficiency. There was no evidence of carcinogenicity with mandipropamid in this study. The NOAEL was 55 mg/kg bw per day.

In a 104-week study, rats were given diets containing mandipropamid at a concentration of 0, 50, 250 or 1000 ppm, equal to 0, 3, 15 or 61 mg/kg bw per day. There were no treatment-related changes in survival or the incidence of tumours. The only significant findings were in males at the highest dose: reductions in body weight, body-weight gain and food conversion efficiency, gross and histopathological changes in the kidneys (roughened surface, and increased severity of chronic progressive nephropathy), and associated osteodystrophia fibrosa and histopathological changes in the parathyroid (increased severity of hyperplasia). Mandipropamid was not carcinogenic in this study. The NOAEL was 15 mg/kg bw per day.

Mandipropamid gave negative results in an adequate range of studies of genotoxicity in vitro and in vivo. The Meeting concluded that mandipropamid was unlikely to be genotoxic.

On the basis of the absence of carcinogenicity in rodents and the absence of genotoxicity, the Meeting concluded that mandipropamid is unlikely to pose a carcinogenic risk to humans.

In a multigeneration study of reproductive toxicity in rats, the target organ was also the liver. No reproductive effects were observed. The NOAEL for parental systemic toxicity was 250 ppm, equal to 22.9 mg/kg bw per day, on the basis of slightly lower body weight and body-weight gain in F_1 males during premating and increased absolute and relative liver weights in male and female parental animals sexes and in F_1 females. The NOAEL for reproductive toxicity was 1500 ppm, equal to 146.3 mg/kg bw per day, the highest dose tested. Toxicity observed in offspring at 1500 ppm included decreased pup weight from day 15 of lactation, increased liver weights in both generations and an increased time to preputial separation in male F_1 pups. The NOAEL for offspring toxicity was 250 ppm, equal to 22.9 mg/kg bw per day.

In a study of developmental toxicity in rats, the NOAEL for maternal and developmental toxicity was 1000 mg/kg bw per day, the highest dose tested. No developmental toxicity or teratogenicity was observed. In rabbits, no effects were observed in dams or fetuses at up to the limit dose of 1000 mg/kg bw per day.

In a study of acute neurotoxicity in rats, mandipropamid exhibited no systemic toxicity or evidence of neurotoxicity at 2000 mg/kg bw. In a 13-week study of neurotoxicity in rats, systemic toxicity was observed at 2500 ppm, equal to 192 mg/kg bw per day, as reductions in body weight, body-weight gain and food efficiency. No evidence of neurotoxicity was observed. The NOAEL was 37 mg/kg bw per day.

There were no reports of adverse health effects in manufacturing-plant personnel or in operators and workers exposed to mandipropamid formulations.

The Meeting concluded that the existing database on mandipropamid was adequate to charact erize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.2 mg/kg bw based on the NOAEL of 15.2 mg/kg bw per day, identified on the basis of decreased body weight and kidney effects (increased severity of chronic progressive nephropathy and associated osteodystrophia fibrosa) at 61.3 mg/kg bw per day in the long-term dietary study in rats and using a safety factor of 100.

The Meeting noted that mandipropamid was not acutely toxic after short-term dosing, that there were no adverse findings in a study of acute neurotoxicity and that mandipropamid did not exhibit developmental toxicity. The Meeting concluded that the establishment of an ARfD was unnecessary.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year studies of toxicity and carcinogenicity [a]	Toxicity	500 ppm, equal to 55 mg/kg bw per day	2000 ppm, equal to 223 mg/kg bw per day
		Carcinogenicity[d]	2000 ppm, equal to 223 mg/kg bw per day	—
Rat	Two-year studies of toxicity and carcinogenicity[a]	Toxicity	250 ppm, equal to 15 mg/kg bw per day	1000 ppm, equal to 61 mg/kg bw per day
		Carcinogenicity[d]	1000 ppm, equal to 61 mg/kg bw per day	—
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	250 ppm, equal to 23 mg/kg bw per day	1500 ppm, equal to 146 mg/kg bw per day
		Offspring toxicity	250 ppm, equal to 23 mg/kg bw per day	1500 ppm, equal to 146 mg/kg bw per day
		Reproduction[d]	1500 ppm, equal to 146 mg/kg bw per day	—
	Developmental toxicity[a,b]	Maternal toxicity[d]	1000 mg/kg bw per day	—
		Embryo and fetal toxicity[d]	1000 mg/kg bw per day	—
Rabbit	Developmental toxicity [,b]	Maternal toxicity[d]	1000 mg/kg bw per day	—

		Embryo and fetal toxicity[d]	1000 mg/kg bw per day	—
Dog	90-day and one-year study of toxicity [c]	Toxicity	25 mg/kg bw per day [e]	40 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Capsule administration.

[d] Highest dose tested.

[e] Based on an overall NOAEL from the two studies.

Estimate of acceptable daily intake for humans

0–0.2 mg/kg bw

Estimate of acute reference dose

Unnecessary

Information that would be useful for continued evaluation of the compound

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

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

Absorption, distribution, excretion, and metabolism in mammals	
Rate and extent of oral absorption	Rapid, extent dependent on dose, 67–74% at the lower dose, 30–45% at the higher dose
Distribution	Highest concentrations in the liver and kidney
Potential for accumulation	No evidence
Rate and extent of excretion	High, virtually complete by 168 h
Metabolism in animals	Mainly glucuronidation (> 50% of excreted dose mandipropamid glucuronide)
Toxicologically significant compounds (animals, plants and environment)	Parent
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 5050 mg/kg bw
Rat, LC_{50}, inhalation	> 5.19 mg/L
Rabbit, dermal irritation	Minimal irritation
Rabbit, ocular irritation	Minimal irritation
Mouse, dermal sensitization	Not sensitizing (local lymph node assay)
Short-term studies of toxicity	

Target/critical effect	Liver, body weight
Lowest relevant oral NOAEL	25 mg/kg bw per day (90-day and 1-year study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day study in rats, highest dose tested)
Lowest relevant inhalation NOAEL	No data
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Body weight, kidney, parathyroid
Lowest relevant NOAEL	15 mg/kg bw per day (rats)
Carcinogenicity	Not carcinogenic in rats and mice
Reproductive toxicity	
Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	146 mg/kg bw per day (rats, highest dose tested)
Developmental target/critical effect	None
Lowest relevant developmental NOAEL	1000 mg/kg bw per day (rats, rabbits, highest dose tested)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity and studies of short-term neurotoxicity	No indications of neurotoxicity in studies of acute toxicity or repeat-dose studies
Medical data	
	No occupational or accidental poisoning reported

Summary			
	Value	*Study*	*Safety factor*
ADI	0–0.2	Rat, 2-year study	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

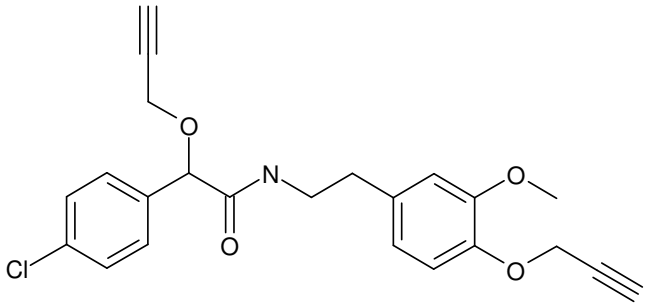
Mandipropamid was considered for the first time by the present Meeting. It belongs to the mandelamide chemical class of fungicides and is a synthetic fungicide intended for the control of Oomycete fungal pathogens in a range of crops.

At the 39th session of the CCPR (ALINORM 07/30/24), it was scheduled for evaluation as a new compound by 2008 JMPR. The Meeting received information on physical and chemical properties, animal and plant metabolism, environmental fate, analytical methods, storage stability, national registered use patterns, supervised residue trials and processing.

The 2008 JMPR established an ADI for mandipropamid of 0–0.2 mg/kg bw/day and concluded that an ARfD was unnecessary.

Mandipropamid is

2-(4-chlorophenyl)-*N*-[3-methoxy-4-(prop-2-ynyloxy)phenethyl]-2-(prop-2-ynyloxy)acetamide



The following abbreviations are used for the metabolites discussed below:

NOA458422	2-(4-Chlorophenyl)-*N*-[2-(4-hydroxy-3-methoxyphenyl)-ethyl]-2-prop-2-ynyl- oxy-acetamide
CGA380778	2-(4-Chlorophenyl)-2-hydroxy-N-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl] -acetamide
SYN521195	2-(4-Chlorophenyl)-*N*-[2-(3-hydroxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop- 2-ynyl-oxy-acetamide
CGA380775	2-(4-Chlorophenyl)-2-hydroxy-*N*-[2-(4-hydroxy-3-methoxyphenyl)-ethyl]-acetamide
SYN500003	(4-Chlorophenyl)-prop-2-ynyloxy-acetic acid
SYN524199	(4-chloro-phenyl)-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2- yloxy)-acetic acid
CGA155705	4-chloro-benzoic acid
SYN 508792	2-(4-chloro-phenyl)-*N*-{2-[3-methoxy-4-(3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-phenyl]-ethyl}-2-prop-2-ynyloxy-acetamide
SYN 508793	malonyl-O-glycoside of NOA 458422
SYN536638	N-[2-(4-Allyloxy-3-methoxyphenyl)-ethyl]-2-(4-chlorophenyl)-2-prop-2- ynyloxy-acetamide

Animal metabolism

The Meeting received information on the fate of orally-dosed mandipropamid in lactating goats.

The principal route of metabolism in goats includes demethylation of the methoxy phenyl functionality to generate the phenol moiety and the removal of either or both of the propargyl side chains to generate the corresponding alcohol or phenol functionalities. The metabolite patterns in the lactating goat and in rats presented qualitatively similar (See the toxicology review in this Report for more details on laboratory animal metabolism).

[^{14}C]mandipropamid, radiolabelled uniformly in either the chlorophenyl or methoxyphenyl ring, was administered orally at doses equivalent to 27–49 mg/kg in the total diet to lactating goats once daily for seven consecutive days. The majority of the radioactivity was excreted in the faeces and urine. For the [^{14}C]chlorophenyl treated goats, 46% of the administered dose was excreted in the faeces and 30% and 33% in the urine. For the remaining goat treated with [^{14}C]methoxyphenyl mandipropamid, 49% of the administered radioactivity was excreted in the faeces and 33% in the urine.

The study results show no significant differences between the metabolic profiles of the two radiolabelled treatments. All metabolites identified contained both the chlorophenyl and

methoxyphenyl moieties, indicating no cleavage of the amide bond between the two aromatic rings. TRRs were low in milk (≤ 0.01 mg/kg), muscle (0.03% TRR, 0.005 mg/kg), and fat (0.01% TRR, ≤ 0.021 mg/kg), and highest in liver (0.11% TRR, 0.48 mg/kg) and kidney (0.01% TRR, 0.13 mg/kg). Unchanged parent mandipropamid comprised the majority of the residue in goat fat (75–77% TRR), and only a small proportion of the residue in goat milk (7.9% TRR) and liver (0.8–1.4% TRR), and was not detected in kidney.

The metabolite NOA 458422 was a significant residue in kidney at 15–18% TRR (0.018–0.024 mg/kg) but was a minor residue in liver at 5.3–5.8% TRR (0.025–0.028 mg/kg). Metabolites CGA 380775, CGA 380778, SYN 505503, SYN 521195, and SYN 518495 were identified as minor residues in kidney (each ≤ 9.3% TRR, < 0.02 mg/kg) and liver (each ≤ 7.3% TRR, ≤ 0.04 mg/kg).

Plant metabolism

The Meeting received plant metabolism studies with mandipropamid on grapes, lettuce, potatoes and tomatoes.

Metabolism studies of mandipropamid in four different crop types (fruit–grapes, leafy vegetables–lettuce, root and tuber vegetables–potato and fruiting vegetables–tomato) demonstrated that metabolism of mandipropamid was similar in the foliar parts, and that the compound undergoes extensive metabolism to form a range of metabolites which are more polar than the parent. Unchanged mandipropamid remained as the major component in all aerial crop parts (ranging from approximately 40% to 94% TRR). A consistent degradation pathway was demonstrated by the four different crop studies though fewer metabolites were identified in lettuce due to a shorter period of exposure to the chemical prior to harvest. In lettuce, grapes, tomatoes and potato leaves, no individual metabolite released by room temperature extraction accounted for > 4.5% TRR mandipropamid equivalents. In peel and flesh of potato tubers, the major metabolite (SYN 500003) accounted for 13% and 11% TRR respectively, but was at very low concentrations (≤ 0.006 mg/kg mandipropamid equivalents).

When grape vines were treated six times with [^{14}C]mandipropamid (chlorophenyl- and methoxyphenyl-label) at a nominal application rate of 150 g ai/ha (1× rate) and 450 g ai/ha (3× rate), parent compound was found as the major component at all time points accounting for 54–80% of TRR. Several additional components (such as NOA 4584422, CGA380778) were detected in the room temperature extracts of the fruit samples of which the largest fraction accounted for a maximum of only 3.8% TRR or 0.040 mg/kg. The metabolite patterns in the overdose studies were very comparable to those found in the 1× rate experiments. The majority of the radioactivity in the fruit was present on the surface, accounting for 79–89% TRR. Of the remaining radioactivity 8–13% TRR was extractable using acetonitrile:water (80:20 v/v) leaving a maximum of 9% TRR unextracted. The majority of the radioactivity (83–91% TRR) in the leaves was extractable using acetonitrile:water (80:20 v/v) leaving a maximum of 17% unextracted. Parent mandipropamid was identified as the major component of the residue in all fruit samples from both labels, ranging from 79 to 80% TRR in the 0 day PHI samples and reducing to 54–59% TRR in the 28 day PHI samples.

When lettuce plants were treated twice with [^{14}C]mandipropamid (chlorophenyl- and methoxyphenyl-label) at a nominal recommended application rate of 150 g ai/ha, parent mandipropamid was the largest component of the residue accounting for 82–94% TRR. Four metabolites were identified, all of which contained both the chlorophenyl and methoxyphenyl rings. NOA458422 and CGA380778 were present both as free metabolites at maximum levels of 1.1% TRR (0.018 mg/kg) and also as conjugated metabolites at maximum levels of 0.4% TRR (0.005 mg/kg). SYN521195 and CGA380775 were only present as conjugated metabolites at maximum levels of 0.2% TRR (0.003 mg/kg). No significant difference was found between the profiles of lettuce samples derived from the two radiolabelled experiments.

Six foliar applications of [chlorophenyl-(U)-^{14}C]mandipropamid or [methoxyphenyl- (U)-^{14}C]mandipropamid were made to potato plants at a rate of 150 g ai/ha. TRRs in peel and flesh

samples were 0.040–0.59 mg/kg and were comparable with both labels and at both PHIs (7 and 21 days). TRRs in potato leaves were much higher, ranging from 2.7–6.3 mg/kg. No significant difference was found between the profiles of the leaf samples derived from the two radiolabelled experiments. Parent mandipropamid was identified as the largest component of the residue in the leaves accounting for 40–61% TRR. Three other metabolites all containing both the chlorophenyl and methoxyphenyl rings (NOA458422, CGA380775 and CGA380778) were identified at much lower levels than parent ranging from 0.4–1.8% TRR. A significant difference was found between the profiles of the peel and flesh samples derived from the two radiolabel experiments; however within each experiment the peel and flesh profiles were similar. Parent mandipropamid was identified in the peel samples at a maximum level of 4.2% TRR (0.002 mg/kg) but was not detected in the flesh. Three small acidic molecules, containing only the chlorophenyl ring, were identified in both the peel and flesh samples. These were SYN500003, SYN524199 and CGA155705 and were detected at maximum levels of 13% TRR, 7.2% TRR and 2.1% TRR respectively (maximum individual residue level of only 0.006 mg/kg). No metabolites containing only the methoxyphenyl ring were identified. Radioactivity remaining in the debris after initial extraction was further investigated using an acidic microwave extraction. A significant proportion of the radioactivity was solubilized and was shown to be mainly comprised of glucose (10–30% TRR) and a second component (7–16% TRR) proposed to be an intermediate breakdown product formed during the acid hydrolysis of starch.

Tomato plants were treated with four foliar applications of [^{14}C]mandipropamid (chlorophenyl- and methoxyphenyl-label) at a rate of 276 g ai/ha and 295 g ai/ha at 2 week intervals, followed by two further treatments at a rate of 147 g ai/ha and 149 g ai/ha in weekly intervals, resulting in a total use rate of 867 g ai/ha. Tomato fruits and leaves/foliage were harvested at 5 intervals: 0, 3, 7, 14 and 28 days after the last application (DALA). Parent compound was the major residue in fruits (61–80% TRR) and leaves (66–76% TRR). Most of the applied radioactivity remained on the surface of the fruits (69–87% TRR). Five metabolites were identified by co-chromatography with reference standards or by LC-NMR and LC-MS as CGA 380775, CGA 380778, NOA 458422, SYN 508792 and SYN 508793 and were present in a range of 0.003 mg/kg and 0.013 mg/kg.

Environmental fate in soil

The Meeting received information on the environmental fate of mandipropamid in soil, including studies on aerobic soil metabolism and crop rotational studies.

Aerobic soil metabolism

Numerous soil studies were performed, under laboratory conditions, to evaluate the route and rate of [^{14}C]mandipropamid labelled in the chlorophenyl ring or the methoxyphenyl ring. Degradation in a wide range of soil types (pH, organic matter, texture, origin) under varying test (temperature, concentration of active ingredient, soil humidity) and incubation conditions (aerobic, anaerobic, microbially active, sterile) were evaluated. The formation and degradation of non-extractable (bound) residues and mineralisation to carbon dioxide represent the main overall pathway for the metabolism of parent compound in soil. In active soils, mandipropamid residues were readily mineralized to [^{14}C]carbon dioxide and accounted for up to 9–45% of applied radioactivity after 120 days (average from 21 studies = 23%), and resulted in non-extractable soil residue levels that reached maximum levels at up to 19–44% of applied radioactivity after 120 days (average from 21 studies = 33%). In less active soils, the mineralization rate to carbon dioxide was lower. A number of metabolites were observed in aerobic degradation studies following the degradation of mandipropamid, namely CGA380778 (≤ 6.0%), NOA458422 (≤ 1.7%) and CGA380775 (< 1%), SYN536638 (≤ 3.2%) and SYN500003 (< 1%).

Aqueous photolysis

The photolysis study conducted with [methoxyphenyl-(U)-^{14}C]mandipropamid at a concentration of l mg/L in sterile buffer solution at pH 7 and 25 °C. The samples were irradiated for periods up to the equivalent of 17 days summer sunlight. The estimated half-life DT_{50} was 34 h of continuous irradiation. At least 16 degradates were formed, none of which represented > 5% of the applied radioactivity.

Aqueous hydrolysis

The hydrolysis study conducted with [ethyl-1-^{14}C]mandipropamid at a concentration of l mg/L in sterile buffer solution at pH 4, 5, 7 and 9 at 50 °C for seven days and at pH 5, 7 and 9 at 25 °C for 32 days. The recovery for all samples was between 92.7 and 105.7% of the applied radioactivity. No degradation of the test substance was observed under all conditions.

Confined rotational crop

In two outdoor confined rotational crop studies in Switzerland, soil was treated directly with [^{14}C]mandipropamid labelled in the chlorophenyl ring or methoxyphenyl ring. Crops of lettuce, radish and wheat were sown into the treated soil at intervals of 29, 58, 120 and 365 days after treatment and were grown to maturity and harvested. Wheat forage was harvested at 50% maturity. Uptake of residues was quite limited with the only identified components being mandipropamid (≤ 0.023 mg/kg), CGA380778 (≤ 0.009 mg/kg) and NOA458422 (≤ 0.016 mg/kg) all of which were identified in the primary crop metabolism studies. Levels of mandipropamid or any other metabolite in succeeding crops would not be expected to exceed 0.03 mg/kg. Since such low radioactive residues were found in analysed fractions of these rotational crop samples, mandipropamid is not readily taken up by succeeding crops.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of mandipropamid in raw agricultural commodities.

Crop samples were extracted with acetonitrile:water (80:20 v/v), extracts were centrifuged and aliquots diluted with water prior to being cleaned-up using polymeric solid-phase extraction cartridges. Residues of mandipropamid were quantified with HPLC-MS-MS. Method DFG S19 with HPLC-MS/MS was suitable for enforcement for agricultural commodities. LOQ values are at 0.01 mg/kg for various plant matrices.

Numerous recovery data on a wide range of substrates were provided from validation testing of the methods, which showed that the methods were valid over the relevant concentration ranges.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the freezer storage stability of residues of mandipropamid in plant commodities.

Residues were stable (less than 30% disappearance) in various plant matrices (tomatoes, grapes, potatoes, lettuce, cucumbers, wheat and soya bean and processed commodities) for at least up to 1 year when stored frozen at –20 °C.

Residue definition

The composition of the residue in the metabolism studies, the available residue data in the supervised trials, the toxicological significance of metabolites, the capabilities of enforcement analytical

methods and the national residue definitions already operating all influence the decision on residue definition.

As indicated the metabolism of mandipropamid was investigated in grapes, lettuce, potatoes and tomatoes. Except for potato tubers unchanged parent compound formed the major part of the residue in these studies. The cleavage products NOA458422, CGA380778 and CGA380775 were identified or observed in all four crops. All metabolites were of minor importance. The major metabolite (SYN 500003) in potato tubers accounted for up to 13% TRR and was present at very low levels (≤ 0.006 mg/kg). Parent mandipropamid was identified in the peel samples at a maximum level of 4.2% TRR (0.002 mg/kg) but was not detected in the flesh.

A metabolism study on lactating goats showed unchanged parent mandipropamid comprised the majority of the residue in goat fat, and only a small proportion of the residue in goat milk and liver, and was not detected in kidney. The metabolite NOA 458422 was a significant residue in kidney but was a minor residue in liver.

The octanol-water partition coefficient of mandipropamid (log K_{OW} = 3.2) implied that mandipropamid may be fat-soluble. However, in the goat metabolism study, TRR in fat was about four times as high as that in liver and in the rat metabolism study, TRRs in fat and muscle were at similar levels. Based on the above information, the Meeting agreed that mandipropamid is not fat-soluble.

Based on the available comparative plant metabolism studies and lactating goat metabolism studies, the Meeting recommended the following residue definition for mandipropamid:

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for plant and animal commodities*: mandipropamid.*

Results of supervised residue trials on crops

The Meeting received supervised trials data for mandipropamid on grapes, onion, broccoli, cabbages, cucumbers, cantaloupe, summer squash, tomatoes, peppers, mustard greens, lettuce and potatoes.

Grapes

Twelve trials were conducted on grape vines in the USA (maximum GAP: 0.15 kg ai/ha, four applications, 14-day PHI) in 2003. In all trials conducted at the maximum USA GAP, the ranked order of residues, median underlined, were: 0.20, 0.21, 0.22, 0.28, 0.38, 0.43, 0.59, 0.62, 0.63, 0.69, 0.76 and 0.85 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in grapes of 2 and 0.43 mg/kg, respectively.

Spring onions

Three trials were conducted on green onions in the USA (maximum GAP: 0.15 kg ai/ha, three applications, 7-day PHI) in 2004. The ranked order of residues, median underlined, was: 0.25, 0.48 and 1.74 mg/kg.

As there were only three trials in accordance with GAP, it was decided that a maximum residue level should be proposed that was higher than highest residue to allow for possible large uncertainty. The Meeting estimated a maximum residue level and an STMR value for mandipropamid in spring onions of 7 and 0.48 mg/kg, respectively.

Bulb onions, dry

In 2004 eight trials were conducted on bulb onions in the USA at the maximum US GAP (0.15 kg ai/ha, four applications, 7-day PHI). The ranked order of residues, median underlined, were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.02 and 0.04 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in bulb onions (dry) of 0.1 and 0.01 mg/kg, respectively.

Broccoli

In 2004 six supervised trials were conducted on broccoli in the USA at the maximum GAP (0.15 kg ai/ha, four applications, 1-day PHI). The ranked order of residues on broccoli, median underlined, were: 0.29, 0.35, 0.43, 0.44, 0.57 and 0.70 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in broccoli of 2 and 0.435 mg/kg, respectively.

Cabbage, head

In 2004 six supervised trials were conducted on cabbages in the USA (maximum GAP: 0.15 kg ai/ha, four applications, 1-day PHI). The ranked order of residues on cabbage with wrapper leaves, median underlined, was: 0.90, 1.10, 1.11, 1.30, 1.60 and 1.80 mg/kg. The ranked order of residues on wrapper leaves of cabbages and cabbages without wrapper leaves, median underlined, was: 1.90, 2.30, 2.90, 4.20, 5.50 and 5.80 mg/kg and < 0.01, < 0.01, < 0.01, < 0.01, 0.05, 0.31 mg/kg, respectively.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in cabbages of 3 and 0.01 mg/kg respectively.

Cucumbers

In 2004 seven trials were conducted on cucumbers in the USA (maximum GAP: 0.15 kg ai/ha, four applications, 0-day PHI). The ranked order of residues on cucumbers, median underlined, was: 0.01, 0.02, 0.02, 0.02, 0.05, 0.05 and 0.07 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in cucumbers of 0.2 and 0.02 mg/kg, respectively.

Melons

Six trials were conducted on cantaloupe in the USA in 2004 (maximum GAP: 0.15 kg ai/ha, four applications, 0-day PHI). The ranked order of residues, median underlined, was: 0.06, 0.07, 0.11, 0.12, 0.19 and 0.26 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in melons, except watermelon, of 0.5 and 0.115 mg/kg, respectively.

Summer squash

Five trials were conducted on summer squash in the USA 2004 (maximum GAP: 0.15 kg ai/ha, four applications, 0-day PHI). The ranked order of residues, median underlined, was: 0.02, 0.03, 0.04, 0.07 and 0.08 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in squash of 0.2 and 0.04 mg/kg, respectively.

Tomatoes

Eleven trials were conducted on tomatoes in the USA in 2003 and 2004 (maximum GAP: 0.15 kg ai/ha, four applications, 1-day PHI). The ranked order of residues on tomato, median underlined, was: 0.02, 0.03, 0.03, 0.06, 0.06, 0.06, 0.06, 0.08, 0.09, 0.12 and 0.20 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in tomato of 0.3 and 0.06 mg/kg, respectively.

Peppers

Nine trials were conducted on sweet and chilli peppers in the USA in 2003 and 2004 (maximum GAP: 0.15 kg ai/ha, four applications, 1-day PHI). The residues on sweet peppers were 0.04, 0.07, 0.09, 0.12, 0.17 and 0.34 mg/kg, while the residues on chilli peppers were 0.11, 0.22 and 0.38 mg/kg.

As the residues were in the same range, the Meeting agreed to combine all data sets to support a MRL for peppers. The combined residues, in ranked order, median underlined, were: 0.04, 0.07, 0.09, 0.11, 0.12, 0.17, 0.22, 0.34 and 0.38 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in peppers of 1 and 0.12 mg/kg, respectively.

Under consideration of the default concentration factor of 7 for dried chilli pepper, the Meeting estimated a maximum residue level and an STMR value for mandipropamid in dried chilli peppers of 10 mg/kg and 0.84 mg/kg.

Leafy vegetables

Eleven trials were conducted on head and leaf lettuce in the USA in 2005 (maximum GAP on leafy vegetables: 0.15 kg ai/ha, four applications, 1-day PHI). The residues on leaf lettuce, median underlined, were 1.90, 4.50, 5.30, 5.70, 7.80 and 7.90 mg/kg, while the residues on head lettuce without wrapper leaves, median underlined, were: 1.60, 2.70, 3.50, 6.10 and 9.60 mg/kg.

Five trials were conducted on mustard greens in the USA in 2004 (maximum GAP on leafy vegetables: 0.15 kg ai/ha, four applications, 1-day PHI). The ranked order of residues on mustard greens, median underlined, were: 1.20, 4.00, 4.50, 4.50 and 11.5 mg/kg.

Six trials were conducted on spinach in the USA in 2005 (maximum GAP on leafy vegetables: 0.15 kg ai/ha, four applications, 1-day PHI). The residues on spinach, median underlined, were: 5.60, 8.20, 9.90, 10.2, 10.9 and 11.0 mg/kg.

The Meeting noted that the residue data populations, following treatment according to US GAP for leafy vegetables were similar, on head and leaf lettuce, mustard greens and spinach, and could be combined. The combined residues, in ranked order, median underlined, were: 1.20, 1.60, 1.90, 2.70, 3.50, 4.00, 4.50 (3), 5.30, 5.60, 5.70, 6.10, 7.80, 7.90, 8.20, 9.60, 9.90, 10.2, 10.9, 11.0 and 11.5 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in leafy vegetables of 25 and 5.65 mg/kg respectively.

Celery

Six trials were conducted on celery in the USA in 2005 (maximum GAP: 0.15 kg ai/ha, four applications, 1-day PHI). The residues on celery, median underlined, were: 0.74, 1.60, 1.80, 3.60, 6.40 and 7.80 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for mandipropamid in celery of 20 and 2.70 mg/kg, respectively.

Potato

The Meeting received information on supervised residue trials on potatoes in France, Germany, Italy, the Netherlands, Spain, Switzerland and the UK.

Supervised trials were conducted on potato, in Germany (maximum GAP, 0.15 kg ai/ha, four applications, 7-day PHI), in France (no GAP provided), in Italy (no GAP provided), in the Netherlands (maximum GAP: 0.15 kg ai/ha, six applications, no PHI) and in Spain (no GAP provided), in Switzerland (no GAP provided), in the UK (maximum GAP: 0.15 kg ai/ha, four applications, 3-day PHI) in 2002, 2003 and 2004.

The Meeting noted that residues in the tuber were below the LOQ (< 0.01 mg/kg) in all trials conducted in France (six trials), Germany (one trial), Italy (one trial), the Netherlands (one trial), Spain (three trials), Switzerland (three trials), the UK (two trials), and agreed to combine all data from the 17 trials utilizing the British GAP. The Meeting estimated a maximum residue level and an STMR value for mandipropamid in potato of 0.01* and 0.01 mg/kg, respectively.

Animal feedstuffs

Wrapper leaves of head cabbage

Six supervised trials were conducted on cabbage in the USA in 2004 (described above). The ranked order of residues on cabbage wrapper leaves, median underlined, were: 1.90, 2.30, 2.90, 4.20, 5.50 and 5.80 mg/kg.

The Meeting estimated an STMR and a high residue values for mandipropamid in wrapper leaves of cabbage of 3.55 and 5.80 mg/kg, respectively.

Fate of residues during processing

The Meeting received information on the fate of mandipropamid residues during aqueous hydrolysis under conditions of pasteurization and baking, brewing, boiling and sterilisation. Information was also provided on the fate of mandipropamid residues during the processing of grapes and tomatoes.

Mandipropamid was stable during the simulation of pasteurization (pH 4, 90 °C), baking, boiling, brewing (pH 5, 100 °C) or sterilisation (pH 6, 120 °C).

The processing factors for raisins (3.91), wet pomace (2.51), dry pomace (6.82), wine (0.85) and juice (0.33) were applied to the estimated STMR for grapes (0.43 mg/kg) to produce STMR-P values for raisins (1.68 mg/kg), wet pomace (1.16 mg/kg), dry pomace (2.93 mg/kg), wine (0.366 mg/kg) and grape juice (0.14 mg/kg). The processing factor for raisins (3.91) was applied to the grape residue data (highest value 0.85 mg/kg) to produce an estimated highest value for dried grapes (3.32 mg/kg).

The Meeting estimated a maximum residue level for mandipropamid in dried grapes (currants, raisins, sultanas) of 5 mg/kg.

The processing factors for wet pomace (0.95), dry pomace (4.45), juice (0.98), puree (1.14) and canned tomatoes (0.36) were applied to the estimated STMR for tomatoes (0.06 mg/kg) to produce STMR-P values for wet pomace (0.057 mg/kg), dry pomace (0.27 mg/kg), juice (0.059 mg/kg), puree (0.068) and canned tomatoes (0.022).

Farm animal dietary burden

The Meeting estimated the dietary burden of mandipropamid in farm animals on the basis of the diets listed in the Annex 6 of the 2006 JMPR Report. Calculation from highest residue and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry

matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, poultry (layer and broiler) are provided in Annex 6. The calculations were made according to the animal diets from the US–Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

The calculations are then summarized and the highest dietary burdens (underlined) are selected for MRL and STMR estimates on animal commodities.

		Animal dietary burden, mandipropamid, ppm of dry matter diet		
		US–Canada	EU	Australia
Beef cattle	Max	0.02	7.75	1.56
	Mean	0.02	4.75	0.73
Dairy cattle	Max	0.01	7.75[a]	1.56
	Mean	0.13	4.75[b]	0.73
Poultry - broiler	Max	0	1.94[c]	0
	Mean	0	0.01	0
Poultry - layer	Max	0	1.94	0
	Mean	0	1.19[d]	0

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

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

[c] Highest maximum poultry broiler and layer dietary burden suitable for MRL estimates for poultry meat and eggs.

[d] Highest mean poultry broiler and layer dietary burden suitable for STMR estimates for milk.

Farm animal feeding studies

No animal feeding studies on ruminants are available. The lactating goat metabolism study was used to evaluate the dietary burden for ruminants. In the metabolism study, in which [^{14}C]mandipropamid equivalent to 27 – 49 ppm in the diet was orally administered to lactating goats for 7 consecutive days, highest residue parent compound (0.019 mg/kg) was found in fat. Given the low estimated animal burden (about one fourth of the administered level), no parent compound is expected to be present more than 0.005 mg/kg in tissues or milk.

For poultry, no feeding and metabolism studies are available. In addition, no analytical method for animal commodities was submitted for mandipropamid in animal commodities. The Meeting agreed that no maximum residue level could be estimated for animal commodities.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of mandipropamid resulted in recommendations for MRLs and STMR values for raw and processed commodities. Data on consumption were available for 17 food commodities and were used to calculate dietary intake. The results are shown in Annex 3.

The International Estimated Daily Intakes (IEDIs) of mandipropamid, based on the STMRs estimated for 17 commodities, were 0–3% of the maximum ADI of 0.2 mg/kg bw for the thirteen GEMS/Food regional diets. The Meeting concluded that the long-term intake of residues of mandipropamid resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The 2008 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of mandipropamid residues is unlikely to present a public health concern.