5.23 MCPA (257)

TOXICOLOGY

MCPA is the ISO-approved common name for 4-chloro-*o*-tolyloxyacetic acid (IUPAC) (CAS No. 94-76-6). MCPA is a selective, systemic, hormone-type herbicide belonging to the phenoxyacetic acid family. It is used to control annual and perennial weeds in cereals, grassland and turf. MCPA has not previously been evaluated by JMPR and was reviewed by the present Meeting at the request of CCPR.

Studies on the 2-ethylhexyl ester (2-EHE) (CAS No. 29450-45-1) and dimethylamine (DMA) (CAS No. 2039-46-5) salt of MCPA were also evaluated. For comparative purposes, and because both preparations convert to MCPA ion prior to gastrointestinal absorption, doses of MCPA 2-EHE and MCPA DMA are expressed as MCPA acid equivalents.

All critical studies contained certificates of compliance with principles of GLP or good clinical practice and the Declaration of Helsinki, as appropriate.

Biochemical aspects

In studies conducted in rats, dogs and humans using either radiolabelled or unlabelled MCPA, MCPA 2-EHE or MCPA DMA, the time to reach the maximum plasma concentration of radioactivity or of MCPA ion ranged from 1 to 8 hours, depending on the dose. In rats, gastrointestinal absorption was at least 95% of the administered dose, with in vitro data suggesting both a saturable carrier-mediated process and a non-saturable process involving simple diffusion. Following oral dosing of rats, there was no evidence of accumulation of radioactivity in any tissues, with the concentrations in the majority of tissues lower than those in blood. In a study conducted in pregnant rats, the concentration of radioactivity in fetal plasma and amniotic fluid was approximately 3- to 9-fold lower than that in maternal plasma.

MCPA, like other organic acids, is excreted via the kidneys by an active mechanism, with this process saturated at sufficiently high doses in rats, dogs and humans; the threshold of renal saturation is lower in dogs than in rats and humans. In rats, excretion of radioactivity was predominantly via the urine (approximately 90% of the administered dose), with relatively low levels detected in faeces (approximately 5% of the administered dose), although increasing the dose from 5 to 100 mg/kg bw increased the level of radioactivity in the faeces of females (approximately 20% of the administered dose). A different pattern of excretion was evident in dogs, with a greater proportion of radioactivity detected in faeces (17% of the administered dose at 5 mg/kg bw and 49% at 100 mg/kg bw). The plasma elimination half-life was longer in dogs (approximately 45 hours) than in rats and humans (approximately 6–10 hours), with this slower elimination resulting in higher systemic exposure at comparable doses. As a consequence of its longer residence time, MCPA ion undergoes more extensive metabolism in dogs. MCPA ion was the predominant compound detected in rat and dog excreta, followed by 4-chloro-2-hydroxymethyl phenoxyacetic acid (HMCPA) and glycine-conjugated MCPA. The proportions of MCPA and HMCPA in rat urine ranged from about 51% to 80% and from about 6% to 16% of the administered dose, respectively. In rat faeces, MCPA and HMCPA accounted for approximately 1–2% and 1–7% of the administered dose, respectively. In dogs, MCPA (up to approximately 30% of the administered dose) and HMCPA (up to approximately 15% of the administered dose) were detected in urine, in addition to a glycine and taurine conjugate (up to 38% and 11% of the administered dose, respectively). In dog faeces, MCPA and the glycine and taurine conjugates were identified (up to 28%, 4% and 19% of the administered dose, respectively).

MCPA induced a variety of drug metabolizing enzymes in rats at relatively high oral doses (100–300 mg/kg bw) and increased fatty acid β-oxidation and the number of hepatic peroxisomes. MCPA's peroxisome proliferating potential was not overtly expressed at lower doses in rodents, with a decrease in serum triglycerides the most consistent finding.

Toxicological data

Acute toxicity studies were conducted with MCPA, MCPA 2-EHE and MCPA DMA. The oral LD_{50} in rats was 500–1200 mg/kg bw, depending on the vehicle. Clinical signs generally occurred within hours of dosing and included piloerection, apathy, hunched posture, abnormal gait, decreased respiration, ptosis, pallor and occasionally ataxia, twitching and tonic convulsions; survivors recovered within about 2 days. The dermal LD_{50} in rats and rabbits was greater than 2000 mg/kg bw, whereas the LC_{50} in rats was greater than 4.5 mg/L. Nil to slight skin irritation and slight to severe eye irritation occurred in rabbits, depending on the formulation. No skin sensitization occurred in guinea-pigs (maximization, open epicutaneous and Buehler tests).

The target organs for MCPA ion are the kidney, liver and blood. In laboratory animals, toxicity following repeated dosing typically manifested as perturbations in clinical pathology parameters (increased serum creatinine, urea, liver enzymes and clotting time and reduced red cell parameters and serum protein) and, in some species, increased kidney and liver weights in conjunction with histopathological changes in these organs. Reduced body weight gain and feed consumption, clinical signs and deaths also occurred.

Short-term studies of toxicity of less than 12 months' duration using MCPA, MCPA 2-EHE or MCPA DMA were performed in rats and dogs. In a 3-month study in rats, the NOAEL was 150 ppm (equal to 12 mg/kg bw per day) for increased serum creatinine and kidney weight at 450 ppm (equal to 35 mg/kg bw per day). In dogs, the overall NOAEL from five studies of 13 or 52 weeks' duration was 6 ppm (equal to 0.2 mg/kg bw per day) for increased serum creatinine and urea and increased pigmentation in the proximal tubules at 30 ppm (equal to 1 mg/kg bw per day).

Long-term studies of the toxicity and carcinogenicity of MCPA were conducted in mice and rats, with no indication of any treatment-related neoplastic lesions up to dietary concentrations of 500 and 320 ppm, respectively (equal to 100 and 20 mg/kg bw per day, respectively). The chronic NOAEL in mice was 100 ppm (equal to 16 mg/kg bw per day) for increased kidney weight and an increased incidence of intratubular calcification, hyaline casts and tubular epithelial hyperplasia at 500 ppm (equal to 83 mg/kg bw per day). The chronic NOAEL in rats was 80 ppm (equal to 5 mg/kg bw per day), based on increased kidney weight and slight increases in the severity of chronic progressive nephropathy in males and haemosiderin deposition in the spleen of both sexes at 12 but not 24 months at 320 ppm (equal to 19 mg/kg bw per day), findings considered to be of questionable relevance.

The Meeting concluded that MCPA is not carcinogenic in mice or rats.

The genotoxicity of MCPA, MCPA 2-EHE and MCPA DMA has been extensively tested in vitro and in vivo, and all were found to have no genotoxic potential. The Meeting concluded that the MCPA ion is unlikely to be genotoxic to humans.

In the absence of genotoxicity potential and a carcinogenic response in mice and rats, the Meeting concluded that MCPA ion is unlikely to pose a carcinogenic risk to humans.

In multigeneration studies in rats on MCPA or MCPA 2-EHE, there was no evidence of reproductive toxicity up to the highest tested dietary concentrations of 1600 and 450 ppm (equal to 150 and 40 mg/kg bw per day, respectively) over one or two generations, respectively. In the two-generation study on MCPA, the NOAEL for parental and offspring toxicity was 150 ppm (equal to 12 mg/kg bw per day) for reduced body weight gain at 450 ppm (equal to 40 mg/kg bw per day). The LOAEL for parental toxicity in this study is consistent with those in four subchronic rat studies. In one-generation studies on MCPA or MCPA 2-EHE, reduced parental body weight gain occurred at the lowest tested dietary concentrations of 450 and 700 ppm (equal to 40 and 65 mg/kg bw per day, respectively), whereas the NOAEL for offspring toxicity was 750 or 700 ppm (equal to 115 and 100 mg/kg bw per day, respectively) for reduced body weight gain at 1000 or 1600 ppm (equal to 160 and 230 mg/kg bw per day, respectively).

In rat developmental toxicity studies conducted on MCPA, MCPA 2-EHE and MCPA DMA, the overall NOAEL for maternal toxicity and fetal and embryo toxicity was 60 mg/kg bw per day for reduced maternal body weight gain and feed consumption, reduced fetal body weight and an increase

in fetal anomalies (mainly delayed ossification), post-implantation losses and early resorptions at 120 mg/kg bw per day. The reduction in maternal body weight gain and feed consumption was evident 1 or 2 days after the commencement of dosing and persisted throughout gestation. The Meeting noted that the developmental findings occurred only at maternally toxic doses.

In a rabbit developmental toxicity study on MCPA, no developmental effects occurred up to the highest tested dose of 60 mg/kg bw per day. The NOAEL for maternal toxicity was 15 mg/kg bw per day, based on clinical signs (piloerection, no defecation and blood in the bedding) and deaths at 30 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 60 mg/kg bw per day, the highest dose tested.

The Meeting concluded that MCPA ion is not teratogenic in rats or rabbits.

Acute and subchronic neurotoxicity studies were conducted on MCPA, MCPA 2-EHE and MCPA DMA in rats. In the acute studies, clinical signs of toxicity observed 24 hours after dosing and transiently impaired motor activity were attributable to acute systemic toxicity rather than to a direct neurotoxic effect. No pathology of the brain or nervous tissue was observed in these or other toxicity studies. The acute NOAEL for MCPA was 150 mg/kg bw, whereas clinical signs (mainly ataxia) were observed at the lowest tested doses of MCPA 2-EHE and MCPA DMA (160 and 143 mg/kg bw, respectively). The overall NOAEL in the three subchronic studies was 4 mg/kg bw per day, with increased serum creatinine the most consistent effect seen at the next higher dose of 30–40 mg/kg bw per day.

4-Chloro-2-carboxyphenoxyacetic acid (CCPA) is a metabolite of MCPA specific to plants. The oral LD_{50} in rats was greater than 2000 mg/kg bw. CCPA was not mutagenic. In a 4-week dietary study, CCPA was approximately 5-fold less toxic than MCPA. The NOAEL for CCPA was 176 mg/kg bw per day, based on reduced serum albumin, increased serum magnesium, increased urine specific gravity and increased renal calcification at approximately 1100 mg/kg bw per day. The LOAEL for MCPA was approximately 170 mg/kg bw per day. The Meeting concluded that CCPA was less toxic than MCPA ion.

Poisoning case reports described clinical observations in humans following deliberate ingestion of relatively large doses of MCPA formulations. Clinical signs consistent with those observed in laboratory animals and renal toxicity were reported.

The Meeting concluded that the database on MCPA ion was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting concluded that the dog was an unsuitable surrogate for humans because of its relatively low renal capacity to excrete MCPA ion, leading to higher toxicity than in other species. Therefore, the Meeting established an ADI of 0–0.1 mg/kg bw per day for MCPA ion, based on the overall NOAEL of 12 mg/kg bw per day from four subchronic studies in rats for changes in clinical chemistry parameters indicative of effects on the kidneys at 35 mg/kg bw per day and using a 100-fold safety factor. This overall NOAEL is supported by the NOAEL of 12 mg/kg bw per day for parental and offspring toxicity from the two-generation reproductive toxicity study in rats and the NOAEL of 15 mg/kg bw per day for maternal toxicity in the developmental toxicity study in rabbits. The Meeting considered that this ADI would adequately cover the kidney and spleen effects observed in the 2-year rat study at 19 mg/kg bw per day. The ADI is established for the sum of MCPA and its salts and esters, expressed as MCPA acid equivalents.

The Meeting established an ARfD of 0.6 mg/kg bw for MCPA ion, based on the overall NOAEL for maternal and developmental toxicity of 60 mg/kg bw and using a 100-fold safety factor. At 120 mg/kg bw, maternal body weight gain and feed consumption were reduced within 1 or 2 days after commencement of dosing in three rat developmental toxicity studies, in addition to an increase in early resorptions in two of these studies. The Meeting considered that the maternal toxicity observed in the rabbit developmental toxicity study was an unsuitable basis for the ARfD because it

was not an acute effect. The ARfD is established for the sum of MCPA and its salts and esters, expressed as MCPA acid equivalents.

A toxicological monograph was prepared.

Levels relevant to risk assessment based on studies conducted on MCPA, MCPA 2-EHE and MCPA DMA

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 ppm, equal to 16 mg/kg bw per day	500 ppm, equal to 83 mg/kg bw per day
		Carcinogenicity	500 ppm, equal to 83 mg/kg bw per day[b]	—
Rat	Thirteen-week studies of toxicity[a,c]	Toxicity	150 ppm, equal to 12 mg/kg bw per day	450 ppm, equal to 35 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	450 ppm, equal to 40 mg/kg bw per day[b]	—
		Parental toxicity	150 ppm, equal to 12 mg/kg bw per day	450 ppm, equal to 40 mg/kg bw per day
		Offspring toxicity	150 ppm, equal to 12 mg/kg bw per day	450 ppm, equal to 40 mg/kg bw per day
	Developmental toxicity studies[c,d]	Maternal toxicity	60 mg/kg bw per day	120 mg/kg bw per day
		Embryo and fetal toxicity	60 mg/kg bw per day	120 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day
		Embryo and fetal toxicity	60 mg/kg bw per day[b]	—

[a] Dietary administration.

[b] Highest dose tested.

[c] Two or more studies combined.

[d] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.1 mg/kg bw

Estimate of acute reference dose

0.6 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 MCPA ion

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and almost complete
Distribution	Widespread tissue distribution
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Rapid except in dogs
Metabolism in animals	Limited; more extensive in dogs

Toxicologically significant compounds in animals, plants and the environment	MCPA, CCPA (plant metabolite)
Acute toxicity	
Rat, LD_{50}, oral	> 500 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.5 mg/L (4 h, whole-body)
Rabbit, dermal irritation	Non-irritating to slightly irritating
Rabbit, ocular irritation	Slightly to severely irritating
Dermal sensitization	Non-sensitizing (guinea-pigs)
Short-term studies of toxicity	
Target/critical effect	Kidney, liver and blood
Lowest relevant oral NOAEL	12 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	160 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Kidney, liver and blood
Lowest relevant NOAEL	16 mg/kg bw per day (mouse)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Target/critical effect	No evidence of reproductive toxicity (rat)
Lowest relevant parental NOAEL	12 mg/kg bw per day
Lowest relevant offspring NOAEL	12 mg/kg bw per day
Lowest relevant reproductive NOAEL	40 mg/kg bw per day (highest dose tested)
Developmental toxicity	
Target/critical effect	Effects on fetuses at maternally toxic doses (rat)
Lowest relevant maternal NOAEL	15 mg/kg bw per day (rabbits)
Lowest relevant embryo/fetal NOAEL	60 mg/kg bw per day (rat)
Neurotoxicity	
Acute and subchronic neurotoxicity	Not neurotoxic
Medical data	
	Effects following human poisonings consistent with laboratory animal findings

Summary

	Value	Studies	Safety factor
ADI	0–0.1 mg/kg bw	Short-term repeated-dose studies (rat), two-generation reproductive toxicity study (rat) and developmental toxicity study (rabbit)	100
ARfD	0.6 mg/kg bw	Developmental toxicity studies (rat)	100

RESIDUE AND ANALYTICAL ASPECTS

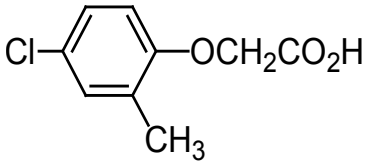
Residue and analytical aspects of MCPA were considered for the first by the present Meeting. It was scheduled for evaluation by the 2012 JMPR by the Forty-third Session of the CCPR.

MCPA is a herbicide in the phenoxyacetic acid class and works by concentrating in the actively growing regions of a plant (meristematic tissue), where it interferes with protein synthesis, cell division and the growth of the plant. It is used for the selective control of broadleaf weeds. MCPA is an acid, but it is usually formulated and applied as a salt, an amine salt or an ester.

The Meeting received information on physical and chemical properties, metabolism, environmental fate, analytical methods and freezer storage stability, national registered use patterns, as well as supervised trials, processing studies and livestock feeding studies.

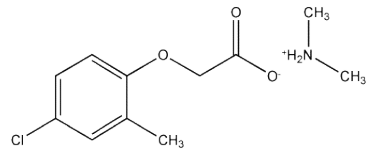
The 2012 JMPR established an ADI for MCPA of 0–0.1 mg/kg bw/day and an ARfD of 0.6 mg/kg bw.

MCPA is 4-chloro-o-tolyloxyaceic acid.

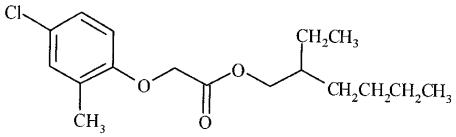


The following compounds are used for the metabolites discussed below:

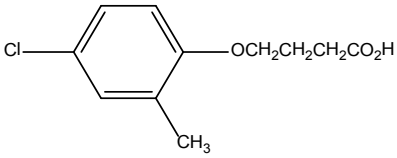
MCPA DMA
(4-chloro-2-methylphenoxyacetic acid) dimethylamine salt



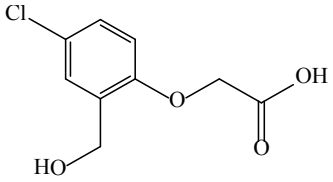
MCPA 2-EHE
2-ethylhexyl (4-chloro-2-methylphenoxy)acetate



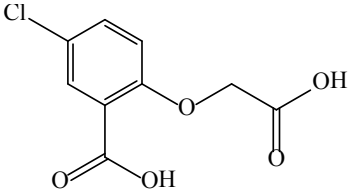
MCPB
4-(4-chloro-2-methylphenoxy) butanoic acid



HMCPA or CHTA
2-hydroxy-4-chlorophenoxyacetic acid



CCPA
2-carboxy-4-chlorophenoxyacetic acid



Animal metabolism

Information was available on metabolism of MCPA in rats, lactating goats and laying hens.

In rats, following oral dose of uniformly ring-labelled [^{14}C]-MCPA, approximately 90% of the administered dose was excreted in urine, with low levels detected in faeces (~5% of the administered dose). MCPA ion was the major compound detected in rat excreta followed by HMCPA and glycine-conjugated MCPA. The proportions of MCPA and HMCPA in rat urine ranged from 51–80% and 6–16% of the administered dose, respectively. In rat faeces, MCPA and HMCPA accounted for approximately 1–2% and 1–7% of the administered dose, respectively. Following oral dosing of rats, there was no evidence of accumulation of radioactivity in any tissues, with the concentration in the majority of tissues lower than in blood.

In a lactating goat study, uniformly ring-labelled [^{14}C]-MCPA was fed to goats for 3 consecutive days at 694 and 832 ppm in feed. Following oral administration, the goats excreted the majority of the dose (99.3%) within 24 hours of dosing, primarily in the urine as unmetabolized MCPA. The primary [^{14}C] component excreted in faeces was also MCPA. Milk and tissues each contained < 0.1% of the total radioactive residues. The small amount of MCPA that is not excreted is

metabolized to the glycine conjugate of MCPA in milk and to an unknown metabolite mainly in liver, kidney, and bile, later identified as composed of three compounds of similar polarity, characterized as triglyceride-like compounds with a dechlorinated MCPA-like structure incorporated by ester or ether linkage.

Unchanged parent MCPA was a significant residue in goat fat (30.2% TRR, 0.042 mg/kg), in milk (28.5% TRR, 0.046 mg/kg), in muscle (22.3% TRR, 0.022 mg/kg) and only a small proportion of the residue in goat kidney (6.7% TRR, 0.060 mg/kg) and liver (4.9% TRR, 0.024 mg/kg).

The conjugate MCPA-glycine was a major residue in milk at 53.9% TRR (0.086 mg eq./kg) but wasn't found in fat, muscle, kidney and liver. Triglyceride-like compounds with a dechlorinated MCPA-like structure were identified as a major residue in fat (30.3% TRR, 0.042 mg eq./kg), kidney (57.4% TRR, 0.509 mg eq./kg) and liver (50.5% TRR, 0.242 mg eq./kg) and as a minor residue in muscle (0.2% TRR, < 0.001 mg eq./kg).

Fifteen laying hens had uniformly ring-labelled [^{14}C]-MCPA administered via feed at 100 ppm for 7 consecutive days, 99.5% of the radioactivity was recovered, primarily as MCPA and acid labile MCPA conjugates in the excreta. The tissues and eggs combined accounted for only 0.04% of the dose administered over 7 days. MCPA was the major component identified in egg white (90.3% TRR, 0.029 mg/kg), egg yolk (57.4% TRR, 0.127 mg/kg), fat (12.0% TRR, 0.004 mg/kg), thigh muscle (35.5% TRR, 0.006 mg/kg) and liver (78.2% TRR, 0.0663 mg/kg). The parent compound was a major component in animal muscle, fat, milk and egg. The metabolism of MCPA in rats, lactating goats and laying hens is qualitatively similar.

Plant metabolism

The Meeting received plant metabolism studies with MCPA on wheat and MCPB on peas.

Metabolism studies of MCPA in two different crops (wheat and peas) demonstrated that metabolism of MCPA was similar, and that the compound undergoes oxidation of the phenyl methyl, and the resulting hydroxymethyl compound forms conjugates, including a glucose conjugate. Further metabolism to the carboxyl compound (CCPA) is also seen.

A wheat metabolism study was conducted with [^{14}C]-MCPA 2-EHE and [^{14}C]-MCPA DMA, labelled with ^{14}C in the ring position. The residue in forage and straw of wheat treated with either form of MCPA was qualitatively similar. A higher proportion of parent MCPA was found in the forage (54.4% TRR, 28.3 mg/kg) and straw (26.6% TRR, 35.9 mg/kg) of wheat for [^{14}C]-MCPA DMA salt. A lower proportion of parent MCPA was found in forage (10.0% TRR, 3.30 mg/kg) and straw (13.7% TRR, 11.3 mg/kg) of wheat for [^{14}C]-MCPA 2-EHE. The residue profiles in grain were similar for either form of MCPA. The main residue in grain was CCPA with a concentration of 25.3% TRR (0.103 mg/kg) for [^{14}C]-MCPA 2-EHE, and 16.5% TRR (0.091 mg/kg) for [^{14}C]-MCPA DMA. Analysis of the hydrolysates of the unextracted residue in forage and straw demonstrated the presence of conjugated forms of MCPA, HMCPA and CCPA. Unextractable residue in grain was subjected to chemical and enzymatic hydrolysis. Analysis of the hydrolysates of bound residue from grain demonstrated the presence of HMCPA and CCPA conjugates. A majority of the resident residue in grain was incorporated into cellular endogenous compounds, primarily glucose, which could be further incorporated into starch or cellulose.

MCPB breaks down into MCPA by the process of β-oxidation. MCPB metabolism study in peas could provide relevant information about the residue pattern of MCPA metabolized in plant. The metabolism of MCPB in peas was investigated using [^{14}C]-MCPB uniformly labelled in the ring position, applied at the rate of 2.26 kg ai/ha. Although the majority of the residues were found in the mature and immature vine, adequate total radioactivity was found in mature pods (0.025 mg eq./kg), seeds (0.024 mg eq./kg) and foliage (4.97 mg eq./kg) to permit extraction and identification of major metabolites. A combination of acetone and acetone/water extracted the majority of the radiolabelled residue from mature vine (92% TRR, 4.57 mg eq./kg) and pod (86% TRR, 0.022 mg eq./kg). Solvents extracted only 38% TRR (0.0092 mg eq./kg) from mature seed. Another 40% TRR (0.0095 mg/kg) was recovered by sequential base and acid hydrolysis. Some of the radiolabelled residue was

identified in mature forage, pod and seed. Mature vine contained mainly the parent, 72% MCPB (3.59 mg/kg), 5.8% MCPA (0.29 mg/kg), and 13% polar unknowns (0.63 mg/kg). Mature pod contained 40% MCPB (0.01 mg/kg), 0.8% MCPA (0.0002 mg/kg) and 48% polar unknowns (0.012 mg/kg). Mature seed contained 1.2% MCPB (0.0003 mg/kg), 11.3% MCPA/MCPA ester (0.0027 mg/kg), 12.5% glucose conjugate of HMCPA (0.003 mg/kg) and about 27% polar unknowns (0.0065 mg/kg). About 29% TRR was unaccounted, including 15% TRR in the residual solid. Based on the study, MCPA and MCPB are the major residues in mature pea vines and pods after treatment of with [^{14}C]-MCPB. The minor residues of MCPB and MCPA were found in grain about 1.2%-4.2% TRR (0.0003-0.001 mg/kg).

Environmental fate in soil

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

Aerobic soil metabolism

The primary hydrolysis rate of ring-labelled [^{14}C]-MCPA 2-EHE was studied in two US soils, a clay loam and a sandy loam. MCPA 2-EHE hydrolysed quickly to MCPA in both soils. Half-life values ranged between 4.5 and 16.6 hours. A further study on aerobic metabolism and degradation of [^{14}C]-MCPA 2-EHE was conducted in a sandy loam soil for 209 days. The calculated half-life was 24 days. A total of 65.6% of applied radioactivity was evolved as volatile radioactivity identified as $^{14}CO_2$ over the 209-day incubation period.

Soil Photolysis

[^{14}C]-MCPA degraded moderately under sunlight. PCOC which is the major degradate did not exceed 5.1% of applied radioactivity. Calculated first order half-lives were 4,718 hours for artificially irradiated soil and 220 hours for naturally irradiated soil.

Confined rotational crop

In a confined rotational crop study in the USA, soil was treated directly with [^{14}C]-MCPA in phenol ring. Crops of lettuce, turnips, and barley were sown into the treated soil at intervals of 30, 120 and 365 days after treatment and were grown to maturity and harvested except for lettuce, which was harvested at intermediate intervals whenever sufficient leaf material could be obtained. [^{14}C]-residues in the top 0–15 cm of soil were 0.276 mg eq./kg on the day of application and declined to 0.045 mg eq./kg by the final barley grain and straw harvest at 582 days after treatment. The decline in soil [^{14}C] residues appeared biphasic with a rapid initial phase (0 to 120 days) having a half-life of 63 days, and a slow secondary phase (120 to 582 days) with a half-life of 511 days. Following application of [^{14}C]-MCPA at 0.84 kg ai/ha, radioactive residues were generally highest in lettuce (0.044 mg eq./kg) at the first harvest from the 120-day plant back interval and lowest in barley grain, turnip roots and tops (< 0.013 mg eq./kg, LOD) at all plant back intervals. For lettuce at the 30-day and 120 day plant-back intervals, residues were greatest at initial sampling (0.029 or 0.044 mg eq./kg), declining to < 0.013 mg eq./kg by the final harvest. For turnip tops and roots and barley grain, residues were non-detectable at all plant-back intervals. Residues in barley forage were detectable at the 30 day plant-back interval (0.017 mg eq./kg), while in barley straw, they were detectable at the 30-day and 120 day plant-back intervals (0.021 and 0.029 mg eq./kg). Residues were all at non-detectable levels at the 365 day plant-back interval. Total MCPA-equivalent residues obtained from rotational crops were below the LOQ at all plant-back intervals. The results of this study indicated that potential for uptake of MCPA residues from the soil by the succeeding crops is low.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of MCPA in raw agricultural commodities, feed commodities and animal commodities.

The crop and animal methods typically use an initial extraction and hydrolysis step, either with acid, base or enzymatic treatment to hydrolyse any esters. After solvent partition and SPE or GPC clean-up, the MCPA, HMCPA and CCPA are methylated ready for GC-MSD analysis or further clean-up before the GC-MSD analysis. After solvent partition and SPE clean-up, reaction with acidic methanol yields the methyl ester and methyl ether derivatives which are analysed by GC/MSD or hydrolysed to MCPA free acid and HMCPA mono-methyl ether for analysis by LC/MS. MCPA residues can be measured in most matrices to an LOQ of 0.01 to 0.05 mg/kg. All methods are considered sufficiently validated for the determination of MCPA, CCPA and HMCPA including conjugates, esters and salts thereof.

The multi-residue method included in the Pesticide Analytical Manual was suitable for enforcement of MCPA residues in a variety of commodities.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of residues of MCPA in plant and animal commodities.

Storage stability studies conducted on cereal and grass commodities demonstrated that MCPA DMA, HMCPA, CCPA and MCPA 2-EHE are stable for up to 12 months in wheat forage, straw and grain, and grass forage and hay samples. MCPA DMA, HMCPA and MCPA 2-EHE are stable up to 17.5 months in wheat flour samples except CCPA stable up to about 14 months. Storage stability studies on cereal green plants, grain and straw showed that MCPA and HMCPA are stable in samples for up to 18 months.

In animal commodities the storage stability studies on MCPA, conducted concurrently with a cattle feeding study, confirmed that residues of MCPA are stable when stored frozen up to at least 4 months in liver and milk, 5 months in kidney and fat, and 3 months in muscle samples. Samples from the metabolism study showed that MCPA and MCPA-glycine (milk only) were stable in frozen storage up to about 46 weeks.

Definition of the residue

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.

A metabolism study showed unchanged parent MCPA comprised the main residue in animal tissues. The major component of residue in milk was MCPA-glycine and wasn't found in any other animal tissues. The Meeting decided that for animal commodities, parent MCPA is the appropriate residue of concern for MRL enforcement, and parent MCPA and its conjugates is the appropriate residue of concern for dietary risk assessment.

The metabolism of MCPA was investigated in wheat and peas. Unchanged parent compound formed the major part of the residue in these studies except wheat grain. CCPA was the major part of residue in wheat grain, but is 5 times less toxic than parent. A certain percentage of the parent residue was present in conjugated form, as uncleaved MCPA 2-EHE (in forage only) or was only released after hydrolysis (forage 15–60%, straw 40–73%, grain 76–85%). Since unconjugated parent MCPA was found in all plant commodities investigated, the Meeting concluded the parent substance is a suitable marker for enforcement purposes in plant commodities and could easily be implemented in multi-residue methods. For dietary intake assessment MCPA-conjugates and esters are easily cleaved and bioavailable. Therefore the Meeting decided to also include conjugates and esters into the residue definition for intake assessment for plant commodities.

The maximum octanol-water partition coefficient of MCPA (log K_{OW} = -0.81–0.71 at pH 7) implied that MCPA may be not fat-soluble. In the goat metabolism study, TRRs in fat and muscle were at similar levels. Based on the above information, the Meeting agreed that MCPA is not fat-soluble.

Definition of the residue (for compliance with the MRL for plant and animal commodities)*: MCPA*.

Definition of the residue (for estimation of dietary intake for plant commodities): *Sum of MCPA, its conjugates and esters, expressed as MCPA*.

Definition of the residue (for estimation of dietary intake animal commodities): *Sum of MCPA and its conjugates, expressed as MCPA*.

The residue is considered as not fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised trials data for MCPA using 2-EHE, DMA salt, sodium salt and potassium salt formulations for barley, wheat, corn, peas (legume vegetable and pulses), flax and grasses. Although the residue definition for compliance with MRLs is MCPA only, the analytical methods used in the supervised trials include hydrolysis steps that release the conjugates and the esters.

The OECD calculator was used as a tool in the estimation of the maximum residue level from the selected residue data set obtained from the supervised trials. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level using expert judgement. Then the OECD calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the Meeting, a brief explanation of the deviation was supplied.

Peas (legume vegetables)

The GAP of the USA for the DMA salt and MCPA Sodium salt, SL formulation, is one spray application at 0.13–0.42 kg ae/ha at 3 node stage up to before flowering. Three trials were carried out in USA in 1996. Residues in green peas without pods were: < 0.01 (3) mg/kg. Three trials were carried out in the USA in 1996 and 2005 in which residues in green peas with pods were: < 0.03 (3) mg/kg.

The Meeting considered the residue data for peas with pods and residue data for peas without pods were insufficient upon which to base a recommendation.

Peas, dry

The GAP for dry peas in the USA (DMA salt and MCPA Sodium salt, SL formulation) is one spray application at 0.13–0.42 kg ae/ha at the 3 node stage up to before flowering.

In eight trials on peas from Canada matching the US GAP residues in dry peas were: < 0.01(8) mg/kg.

The Meeting estimated a maximum residue level and STMR value for MCPA in dry peas of 0.01* and 0 mg/kg, respectively.

Barley and wheat

The GAP for the UK is for one spray application at 1.7 kg ae/ha at BBCH 30(DMA salt SL formulation). Four barley trials were conducted in France and the UK matching the GAP of the UK. In the trials residues in barley grain were < 0.05 (4) mg/kg.

The GAP in Spain (DMA salt SL formulation), is for one spray application at 1.2 kg ae/ha at BBCH 30. Four barley trials were conducted in France and Spain in line with Spanish GAP. The residues in barley were: < 0.05 (3) and 0.12 mg/kg.

The GAP for the UK is for one spray application at 1.7 kg ae/ha at BBCH 31 (DMA salt SL formulation). Five wheat trials were conducted in France and the UK in line with the UK GAP. The residues in wheat were: < 0.05 (4) and 0.16 mg/kg.

The GAP in Spain consists of one spray application at 1.2 kg ae/ha at BBCH 31 (Sodium or potassium salt SL formulation). Four wheat trials were conducted in France and Spain in line with Spanish GAP. Residues found in wheat grain were: < 0.05 (4) mg/kg.

The Meeting noted that MCPA applied to barley and wheat before flowering results in comparable residues and agreed to combine all data from France and the UK against the UK GAP to support a maximum residue level for grain of barley, oats, rye, triticale and wheat. The residues found, median underlined, were: < 0.<u>05</u>(11) and 0.16 mg/kg.

The Meeting estimated a maximum residue level and an STMR in the cereals grains barley, oats, rye, triticale and wheat of 0.2 and 0.05 mg/kg, respectively.

Maize

The GAP of Canada consists of one spray application at 0.55 kg ae/ha (DMA salt SL formulation); one spray application at 0.6 kg ae/ha, at 15 cm height stage (MCPA sodium salt SL formulation). All eight trials in Canada were treated at 1.5× the maximum rate and resulted in non-detectable residues in maize grain: < 0.01(8) mg/kg.

The Meeting estimated a maximum residue level and an STMR for MCPA in maize grain of 0.01* and 0 mg/kg, respectively.

Flax seeds

The GAP of Canada consists of one spray application at 0.41–0.875 kg ae/ha, before bud stage (MCPA 2-EHE EC formulation, DMA salt SL formulation, and MCPA sodium salt SL formulation). In six trials on flax against the Canadian GAP residues in linseeds were: < 0.01(6) mg/kg for MCPA.

The Meeting estimated a maximum residue level and an STMR value for MCPA in flax seeds of 0.01* and 0 mg/kg, respectively.

Animal feedstuffs

Pea forage

The GAP of the USA (DMA salt and MCPA sodium salt, SL formulation), consists of one spray application at 0.13–0.42 kg ae/ha at the 3 node stage up to before flowering. Two trials on pea were carried out in Canada against the US GAP. The ranked order of residues on pea forage was: < 0.25 and 0.42 mg/kg.

The Meeting considered the residue data for peas forage to be insufficient upon which to base recommendations.

Pea hay

The GAP of the USA (DMA salt and MCPA Sodium salt, SL formulation), consists of one spray application at 0.13–0.42 kg ae/ha at 3 node stage up to before flowering. Two trials on pea were carried out in Canada against the US GAP. The residues in pea hay were: 0.74 and 1.97 mg/kg (fresh weight).

The Meeting considered the residue data for pea hay to be insufficient upon which to base a maximum residue level recommendation.

Barley, oats, rye, triticale and wheat forage

The GAP of the UK (DMA salt SL formulation), is one spray application at 1.7 kg ae/ha at BBCH 30. Two trials on barley and wheat each were carried out in France and the UK matching UK GAP. The ranked order of concentrations on barley forage (fresh weight) was: 4.2, 4.3, 7.5 and 23 mg/kg.

The GAP of Spain (DMA salt SL formulation), consists of one spray application at 1.2 kg ae/ha; (MCPA sodium or potassium salt SL formulation), one spray application at 1.2 kg ae/ha, at

BBCH 30 stage. Four trials on barley and wheat were carried out in Spain against Spanish GAP. The residues found on barley forage were: 0.6, 1.1, 1.4 and 5.1 mg/kg.

The GAP of Canada (MCPA 2-EHE EC formulation), is one spray application at 0.35–0.88 kg ae/ha; or one spray application at 0.63–0.88 kg ae/ha (DMA salt SL formulation); or one spray application at 0.45–0.83 kg ae/ha (MCPA sodium salt SL formulation), at 15 cm height stage. The GAP of the USA (MCPA 2-EHE EC formulation and DMA salt SL formulation) consists of one spray application at 0.88 kg ae/ha at early boot stage.

In 25 trials on wheat forage from Canada (15 trials) and the USA (10 trials) at about double the maximum rate of the Canadian or US GAP, residues were: 3.08, 3.18, 3.46, 4.13, 5.38, 5.48, 5.55, 5.82, 6.37, 7.14, 7.15, 7.36, 7.73, 7.94, 8.30, 8.74, 9.02, 9.12, 9.75, 9.79, 11.0, 12.6, 12.8, 13.6 and 21.2 mg/kg

The residues were scaled to the application rates authorised by Canada and the USA were calculated by dividing by 2 (1.85 kg ae/ha / 0.88 kg ae/ha) and were (n = 25): 1.56, 1.57, 1.70, 2.09, 2.45, 2.66, 2.76, 2.89, 3.01, 3.38, 3.81, 3.87, 3.93, 4.09(2), 4.43, 4.51, 4.69, 4.72, 4.91, 5.19, 6.03, 6.59, 7.00 and 9.52 mg/kg.

The Meeting considered the residue data for barley and wheat forage from European trials matching the UK GAP to be insufficient, and agreed to base the estimations on the Canadian dataset and to extrapolate the estimated values to oats, rye and triticale.

The Meeting estimated an STMR and a highest residue values for MCPA in barley, oats, rye, triticale and wheat forage of 3.93 and 9.52 mg/kg.

Maize forage

The GAP of Canada consists of one spray application at 0.55 kg ae/ha (DMA salt SL formulation), or one spray application at 0.6 kg ae/ha at 15 cm height stage (MCPA sodium salt SL formulation). No trials in Canada complied with the Canadian GAP.

The Meeting considered the residue data for maize forage to be insufficient upon which to base an estimate.

Grass forage

The GAP of the USA, consists of either one spray application at 1.6–2.1 kg ae/ha at early bud to full bloom stage (MCPA 2-EHE EC formulation) or, one spray application at 1.7 kg ae/ha when grasses begin to tiller or before heads come to boot stage (MCPA DMA salt, SL formulation). All eight trials on grasses were carried out in the US matched GAP. The residues on grass forage, median underlined, in ranked order were: 16.4, 21.0, 31.0, 40.5, 53.5, 70.2, 94.3 and 108 mg/kg.

The GAP in Spain consists of one spray application at 1.2–1.6 kg ae/ha targeting weeds in active growth stage (DMA salt SL formulation). Four trials on grasses were carried out in France and Spain matching Spanish GAP. The residues in forage were: 3.70, 6.60, 11.0 and 19.0 mg/kg.

The Meeting noted that the US trials resulted in higher residues in grass forage and decided to use the US data to estimate a STMR and a highest residue values for MCPA in grass forage of 47 and 108 mg/kg, respectively.

Grass hay

The GAP of the USA consists of one spray application at 1.6–2.1 kg ae/ha at early bud to full bloom stage (MCPA 2-EHE EC formulation), or one spray application at 1.7 kg ae/ha when grasses begin to tiller or before heads come to boot stage (MCPA DMA salt, SL formulation). Eight trials on grasses were carried out in US matching GAP. The residues on grass hay, median underlined, in ranked order were: 37.4, 40.3, 42.5, 68.0, 80.7, 94.8, 196 and 217 mg/kg (air dry).

Based on an average dry-mass of 88% residues in grass hay (dry weight) were: 42.5, 45.8, 48.3, 77.3, 91.7, 107.7, 222.7 and 246.6 mg/kg.

The Meeting estimated a maximum residue level, an STMR and a highest residue for MCPA in grass hay of 500 mg/kg (DM based), 74.35 mg/kg and 217 mg/kg (air dry), respectively.

Straw and fodder of cereal grain (dry)

Barley, oat, rye, triticale and wheat hay

The GAP of Canada for barley consists of one spray application at 0.35–0.88 kg ae/ha (MCPA 2-EHE EC formulation), or one spray application at 0.63–0.88 kg ae/ha (DMA salt SL formulation), or one spray application at 0.45–0.83 kg ae/ha, at early flag leaf stage (MCPA Sodium salt SL formulation). In two trials in Canada matching the GAP the residues on barley hay were: 5.18 and 6.61 mg/kg.

The GAP in Canada on wheat consists of one spray application at 0.35–0.88 kg ae/ha (MCPA 2-EHE EC formulation); or, one spray application at 0.63–0.88 kg ae/ha (DMA salt SL formulation); or, one spray application at 0.45–0.83 kg ae/ha, at 15 cm height stage (MCPA sodium salt SL formulation). The US GAP on wheat consists of, one spray application at 0.88 kg ae/ha at early boot stage (MCPA 2-EHE EC formulation and DMA salt SL formulation). In 25 wheat trials from Canada (15 trials) and US (10 trials) treated at about 2× the maximum GAP rate of Canadian and the US residues were: 4.25, 6.68, 7.34, 8.09, 10.9, 11.3(2), 13.5, 14.6, 15.7(2), 16.7, 19.8, 20.9, 21.6, 23.3, 26.5, 30.6, 30.7, 30.9, 32.7, 35.5, 49.3, 50.5 and 66.0 mg/kg (air dry).

The residues scaled to the application rates authorised by Canada and the USA were calculated by dividing by 2 (1.85 kg ae/ha / 0.88 kg ae/ha) and were (n = 25): 2.15, 3.03, 3.91, 4.07, 5.00, 5.39, 5.56, 7.12, 7.20, 7.30, 7.85, 8.35, 10.5, 10.8, 11.2(2), 12.5, 14.4, 14.7, 15.8, 16.1, 16.5, 24.3, 26.3 and 28.9 mg/kg.

Barley, oat, rye, triticale and wheat straw

The GAP of the UK is one spray application at 1.7 kg ae/ha at BBCH 30 stage (DMA salt SL formulation). In 12 trials on barley and wheat carried out in Austria, France and the UK matching UK GAP. The residues on barley straw were: < 0.05(3), 0.07, 0.22, 0.28 and 1.04 mg/kg. The residues on wheat straw were: < 0.05(2), 0.05, 0.09 and 0.22 mg/kg.

The GAP of Spain consists of one spray application at 1.2 kg ae/ha (DMA salt SL formulation), or one spray application at 1.2 kg ae/ha, at BBCH 30 stage (MCPA sodium or potassium salt SL formulation). Nine trials on barley were carried out in France and Spain matching Spanish GAP. The residues on barley straw were: < 0.05(4) and 0.24 mg/kg. The residues on wheat straw were: < 0.05(4) mg/kg.

The GAP of Canada on barley consists of one spray application at 0.35–0.88 kg ae/ha (MCPA 2-EHE EC formulation); or, one spray application at 0.63–0.88 kg ae/ha (DMA salt SL formulation); or one spray application at 0.45–0.83 kg ae/ha (MCPA sodium salt SL formulation), at early flag leaf stage In 36 trials matching Canadian GAP the residues on barley straw, median underlined, were: < 0.25(34), 0.25 and 0.29 mg/kg.

The GAP of Canada on wheat consists of one spray application at 0.35–0.88 kg ae/ha (MCPA 2-EHE EC formulation); or one spray application at 0.63–0.88 kg ae/ha (DMA salt SL formulation); or one spray application at 0.45–0.83 kg ae/ha (MCPA sodium salt SL formulation), at 15 cm height growth stage. The GAP of the USA consists of, one spray application at 0.88 kg ae/ha at early boot stage (MCPA 2-EHE EC formulation and DMA salt SL formulations). In wheat trials from Canada (15) and US (10) treatment rates were 2× the maximum rate of Canadian and US GAP. Residues found, in ranked order were: < 0.25(6), 0.31, 0.34, 0.37, 0.42, 0.65, 0.82, 1.16, 1.30, 1.62, 1.72, 1.73, 2.51, 2.99, 3.65, 3.98, 4.93, 5.54, 7.19 and 11.3 mg/kg.

Based on an average dry-mass of 88% residues in wheat hay (dry weight) were: 2.44, 3.44, 4.44, 4.63, 5.68, 6.13, 6.32, 8.09, 8.18, 8.30, 8.92, 9.49, 11.9, 12.3, 12.7(2), 14.2, 16.4, 16.7, 18.0, 18.3, 18.8, 27.6, 29.9 and 32.8 mg/kg.

The Meeting noted that higher residues data came from the scaled datasets at 2× US and Canadian GAPs on wheat hay. Based on wheat hay, the Meeting agreed to estimate a maximum

residue level, a highest residue and an STMR for MCPA on wheat hay of 50 (DW), 28.9 and 10.5 mg/kg, and extrapolate them to straw of barley, oat, rye and triticale.

Maize fodder, dry

The GAP of Canada consists of, one spray application at 0.55 kg ae/ha (MCPA DMA salt SL formulation); or one spray application at 0.60 kg ae/ha (MCPA sodium salt SL formulation), at the 15 cm height stage. Eight trials were carried out in Canada at 1.5× the maximum rate and resulted in residues in maize stover of < 0.25(8) mg/kg.

Based on an average dry-mass of 83%, residues in maize fodder (dry weight) were: < 0.30(8) mg/kg.

The Meeting estimated an STMR and a highest residue for MCPA in maize stover of 0 mg/kg (fresh weight) and recommended a maximum residue level of 0.3 mg/kg for maize fodder, dry.

Fate of residues during processing

The Meeting received information on the fate of MCPA residues during the food processing of wheat grain.

Calculated processing factors are summarized in the following table. Factors are indicated with a "<" (less than) sign when the residue in the processed commodity is below the LOQ of the analytical method. The calculation is then made on the LOQ of the analytical method and the residue concentration of the RAC (raw agricultural commodity).

Processed Fractions	MCPA DMA salt	MCPA 2-EHE	Average process factor	Wheat grain STMR (mg/kg)	STMR-P (mg/kg)
Germ	0.67	0.29	0.48		0.024
Bran	0.67	0.29	0.48	0.05	0.024
Flour	0.67	0.29	0.48		0.024

Residues in animal commodities

Farm animal feeding

The Meeting received lactating dairy cow feeding studies, which provided information on likely residues resulting in animal tissues and milk from residues in the animal diet. Animals were orally administered the equivalent to 50(1×), 150(3×), and 500(10×) ppm in feed on a dry weight basis.

Residues of MCPA in whole milk in the 50, 150 and 500 ppm groups were < 0.01 mg/kg, < 0.01 mg/kg and 0.015–0.023 mg/kg (average values) respectively. In muscle, for the same groups, residues were < 0.05 mg/kg, < 0.05 mg/kg, and < 0.05–0.08 mg/kg respectively. Residues of MCPA in fat were < 0.05 mg/kg, < 0.05–0.17 mg/kg and < 0.05–0.13 mg/kg respectively. Residues of MCPA in liver were < 0.05 mg/kg, < 0.05–0.09 mg/kg and 0.16–0.28 mg/kg respectively. Residues in kidney were 0.28–0.41 mg/kg, 0.60–1.23 mg/kg and 1.66–2.44 mg/kg respectively.

In a hen metabolism study [^{14}C]-MCPA was fed at 100 ppm in the diet for 7 consecutive days. Residue levels in edible tissues and eggs were 0.004 mg/kg in fat, 0.006 mg/kg in muscle, 0.0663 mg/kg in liver, and 0.156 mg/kg in eggs.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and layer are provided in Annex 6. The calculations were made according to the animal diets from US-Canada, EU, Australia and Japan in the OECD Feed Table 2009.

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

	Animal dietary burden, MCPA, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	37.0	12.7	216	94.0	432 [a]	188 [b]	107.9	39.0
Dairy cattle	194.4	84.6	259.2	112.8	432 [c]	188 [d]	191.2	69.5
Poultry-broiler	0.043	0.043	0.04	0.043	0.009	0.009	0.006	0.006
Poultry-layer	0.043	0.043	43.3 [e]	18.9 [f]	0.009	0.009	-	-

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

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

[c] Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk.

[d] Highest mean dairy cattle dietary burden suitable for STMR estimates for mammalian milk.

[e] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

[f] Highest mean poultry dietary burden suitable for STMR estimates for meat and eggs.

Both the highest maximum dietary burden (432 ppm) and the mean dietary burden for cattle (188 ppm) is greater than the actual 3× dose in the feeding study (150 ppm) and lower than the actual 10× dose in the feeding study (500 ppm). The MRL and STMR values were estimated by interpolation of data between dose levels.

Tabulated below are the calculations of maximum residue levels and STMRs for milk and animal tissues.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg/kg) in			
				Muscle	Liver	Kidney	Fat
Maximum residue level beef or dairy cattle							
Feeding study[a]	500/150	0.043/< 0.01	500/150	0.08/0.08	0.28/0.09	2.44/1.20	0.17/0.13
Dietary burden and residue estimate	432	0.035	432	0.08	0.25	2.20	0.16
STMR beef or dairy cattle							
Feeding study[b]	500/150	0.043/< 0.01	500/150	0.08/< 0.08	0.28/0.09	2.44/1.20	0.17/0.13
Dietary burden and residue estimate	188	0.013	188	0.08	0.10	1.33	0.13

[a] Highest residue for tissues and mean residue for milk

[b] Mean residues for tissue and milk

The Meeting estimated maximum residue levels of 0.1 mg/kg for meat from mammals other than marine mammals, 0.2 mg/kg for mammalian fat, 3 mg/kg for mammalian edible offal, and 0.04 mg/kg for milks. The Meeting estimated STMRs of 0.08 mg/kg for meat from mammals other than marine mammals, 0.13 mg/kg for mammalian fat, 1.33 mg/kg for mammalian edible offal, 0.013 mg/kg for milks. The Meeting estimated HRs of 0.08 mg/kg for meat from mammals other than marine mammals, 0.16 mg/kg for mammalian fat and2.20 mg/kg for mammalian edible offal.

Residues in poultry tissues and eggs are estimated using the data from the poultry metabolism study in which the dose rate was 100 ppm and the highest and mean residues in tissues and eggs were determined.

Estimation of residues in poultry tissues and eggs.

	Feed level (ppm) for egg residues	Residues (mg/kg) in egg	Feed level (ppm) for tissue residues	Residues (mg/kg) in		
				Muscle	Liver	Fat
Maximum residue level broiler or layer poultry						
Feeding study[a]	100	0.156	100	0.006	0.0663	0.004

	Feed level (ppm) for egg residues	Residues (mg/kg) in egg	Feed level (ppm) for tissue residues	Residues (mg/kg) in		
				Muscle	Liver	Fat
Dietary burden and residue estimate	43.3	0.068	43.3	0.003	0.029	0.002
STMR broiler or layer poultry						
Feeding study[b]	100	0.156	100	0.006	0.0663	0.004
Dietary burden and residue estimate	18.9	0.029	18.9	0.001	0.0125	0.0008

[a] Highest residue for tissues and mean residue for egg

[b] Mean residues for tissue and egg

The Meeting noted that the LOQ of analytical method is 0.05 mg/kg, and agreed to estimate maximum residue levels of 0.05* mg/kg for poultry meat (fat), poultry edible offal and for eggs. The Meeting estimated STMRs of 0.05 mg/kg for poultry meat, poultry fat, edible offal and for eggs. The Meeting estimated HRs of 0.05 mg/kg for poultry meat, poultry fat, edible offal and for eggs.

DIETARY RISK ASSESSMENT

Long term intake

The evaluation of MCPA resulted in recommendations for MRLs and STMR values for raw and processed commodities. Data on consumption were available for 19 food commodities and were used to calculate dietary intake. The results are shown in Annex 3.

The International Estimated Daily Intakes (IEDIs) of MCPA, based on the STMRs estimated, were 0–1% of the maximum ADI of 0.1 mg/kg bw for the thirteen GEMS/Food cluster diets. The Meeting concluded that the long-term intake of residues of MCPA resulting from its uses that have been considered by JMPR is unlikely present a public health concern.

Short-term intake

The IESTI of MCPA calculated on the basis of the recommendations made by the JMPR ranged from 0–5% of the ARfD (0.6 mg/kg bw). The results are shown in Annex 4.

The Meeting therefore concluded that the short-term intake of MCPA residues, when used in ways that have been considered by the JMPR, is unlikely present a public health concern.