5.19 MESOTRIONE (277)

TOXICOLOGY

Mesotrione is the ISO-approved common name for 2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione (IUPAC), with CAS number 104206-82-8. It is a new triketone herbicide with a 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibition mode of action.

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

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

Biochemical aspects

Excretion and tissue retention studies were performed in mice and rats. In addition, a full set of metabolism studies was performed in rats. Radiolabelled mesotrione was administered by gavage in both species. In mice, mesotrione was extensively absorbed (> 60%) and primarily excreted in the urine, constituting 41–59% of the administered low dose (1 mg/kg bw per day) and 63–70% of the high dose (100 mg/kg bw per day). Faecal elimination comprised 21–38% of the administered dose. Elimination was essentially complete within the first 24 hours; by 72 hours following dosing, elimination comprised 91–95% of the administered dose. In rats, mesotrione is rapidly and extensively absorbed (> 60%), metabolized to a limited extent and excreted primarily in the urine after single low (54–56% at 1 mg/kg bw) or high doses (29–30% at 100 mg/kg bw) or repeated low doses (23–30% at 1 mg/kg bw per day) over 14 days to rats. Biliary excretion was minimal. Most of the radioactivity was excreted as the parent compound within the first 12 hours post-dosing. Highest levels were found in liver, kidneys and gastrointestinal tract in both species, with 10–15% present in tissues following a low dose and less than 0.3% following a high dose.

In studies performed only in rats, there was no evidence of accumulation. C_{max} values were 0.26 and 0.25 µg equiv/g in male and female rats, respectively, at the low dose (1 mg/kg bw) and 40.4 and 19.9 µg equiv/g, respectively, at the high dose (100 mg/kg bw). The T_{max} was 0.5 hour at the low dose and 1.5 hours at the high dose. Half-lives in blood were less than 2 hours, regardless of sex or dose. There were no notable differences in absorption or excretion between the sexes. Mesotrione and its metabolites were not excreted in expired air. Parent compound accounted for more than 43–64% of the administered dose in the urine and 0–8% of the administered dose in the faeces.

In rats, the metabolites produced from hydroxylation of the dione ring include 4-hydroxy-mesotrione, 5-hydroxy-mesotrione, 2-nitro-4-(methylsulfonyl)-benzoic acid (MNBA) and 4-(methylsulfonyl)-2-aminobenzoic acid (AMBA). There is also a proposed cleavage of the molecule into constituent rings and reduction by the gut microflora, resulting in a number of unidentified metabolites, accounting for a total of approximately 0–12% of the administered dose in the faeces.

Toxicological data

In the rat, mesotrione is of low acute oral toxicity (LD_{50} > 5000 mg/kg bw), low acute dermal toxicity (LD_{50} > 2000 mg/kg bw) and low acute inhalation toxicity (LC_{50} > 4.75 mg/L). In the rabbit, mesotrione was non-irritating to the skin and mildly irritating to the eyes. Mesotrione was not a dermal sensitizer in guinea-pigs (maximization test).

The primary effect of mesotrione in mammals is the inhibition of HPPD, a key enzyme of the tyrosine catabolic pathway. Inhibition of HPPD by mesotrione results in raised plasma tyrosine levels, which appear to be responsible for the critical effects observed (ocular, kidney, liver and thyroid toxicity). The plateau levels of plasma tyrosine after mesotrione administration are higher in rats (males > females) than in mice. The difference in sensitivity between male and female rats as

well as between rats and mice can be attributed to differences in tyrosine catabolism. If the activity of tyrosine aminotransferase (TAT) is low, as it is in the male rat, tyrosine cannot convert quickly to 4-hydroxyphenylpyruvate (HPP); when HPPD is inhibited, the resultant increase in plasma tyrosine levels leads to toxicity.

The critical effect (ocular toxicity) associated with the administration of mesotrione is mediated by these increased systemic levels of tyrosine and occurs only when plasma tyrosine levels exceed about 1000 nmol/mL. The ocular sensitivity of the various species to tyrosine plasma levels seems to be similar; the difference in overall toxicity of mesotrione among the species is attributable to the different levels of plasma tyrosine achieved after HPPD inhibition by mesotrione.

Although the rat is the most sensitive species for assessing tyrosine-mediated mesotrione toxicity, the mouse is a better model for such effects in humans. Humans and mice have similar TAT activities and do not experience the adverse effects associated with the same degree of HPPD inhibition in rats. The effects on the eyes, kidneys, liver and thyroid seen in the rat are unlikely to occur in humans exposed to mesotrione owing to differences in tyrosine metabolism. As all the relevant studies normally performed in the rat were also performed in the mouse, it was determined that the risk assessment would be based on toxicity in the mouse, rabbit and dog.

In a 90-day oral toxicity study in mice, animals were given diets containing mesotrione at a concentration of 0, 10, 50, 350 or 7000 ppm (equal to 0, 1.7, 8.4, 61.5 and 1212.4 mg/kg bw per day for males and 0, 2.4, 12.4, 80.1 and 1537.1 mg/kg bw per day for females, respectively). The NOAEL was 7000 ppm (equal to 1212.4 mg/kg bw per day), the highest dose tested.

In a 90-day oral toxicity study in rats, animals were given diets containing mesotrione at a concentration of 0, 1, 125, 1250 or 12 500 ppm (equal to 0, 0.09, 10.96, 112.09 and 1110.86 mg/kg bw per day for males and 0, 0.10, 12.81, 125.58 and 1212.53 mg/kg bw per day for females, respectively). At 125 ppm (equal to 10.96 mg/kg bw per day), male rats showed evidence of increased corneal opacity and vascularization and decreased body weight and feed efficiency.

In a 13-week oral toxicity study in rats, animals were given diets containing mesotrione at a concentration of 0, 2.5, 5.0, 7.5 or 150 ppm (equal to 0, 0.21, 0.41, 0.63 and 12.46 mg/kg bw per day for males and 0, 0.23, 0.47, 0.71 and 14.48 mg/kg bw per day for females, respectively). There were no non-ocular findings in either male or female rats in this study. At 7.5 and 150 ppm, males showed evidence of cloudy eyes.

In a 13-week oral capsule toxicity study in dogs, animals were exposed to 0, 100, 600 or 1000 mg/kg bw per day. At 1000 mg/kg bw per day, body weights were decreased in males compared with controls and there was an increase in minimal/slight focal mesothelial proliferation of the atrium of the heart in two males. The NOAEL was 600 mg/kg bw per day.

In a 1-year oral capsule toxicity study in dogs, animals were exposed to 0, 10, 100 or 600 mg/kg bw per day. At the high dose, body weights were decreased in females, and lenticular opacity was observed in one male and one female. In the male, the lenticular opacity was associated with unilateral keratitis and periorbital haemorrhage; in the female, it was associated with unilateral corneal erosion. The NOAEL was 100 mg/kg bw per day.

In a 1-year oral toxicity study in mice, animals were given diets containing mesotrione at a concentration of 0, 10, 50, 350 or 7000 ppm (equal to 0, 1.5, 7.8, 56.2 and 1114 mg/kg bw per day for males and 0, 2.1, 10.3, 72.4 and 1494.5 mg/kg bw per day for females, respectively). At the highest dose tested, males exhibited decreased body weight and body weight gains. There were no effects in females at the highest dose tested. The NOAEL was 350 ppm (equal to 56.2 mg/kg bw per day).

In an 18-month oral toxicity and carcinogenicity study in mice, animals were given diets containing mesotrione at a concentration of 0, 10, 350 or 3500/7000 ppm (equal to 0, 1.4, 49.7 and 897.7 mg/kg bw per day for males and 0, 1.8, 63.5 and 1102.9 mg/kg bw per day for females, respectively). As seen in the 1-year study, body weight, body weight gains and feed efficiency were decreased in males at the highest dose tested, and there were no effects in females at the highest dose

tested. There was no evidence of carcinogenicity. The NOAEL was 350 ppm (equal to 49.7 mg/kg bw per day).

In a 2-year carcinogenicity study in rats, animals were given diets containing mesotrione at a concentration of 0, 7.5, 100 or 2500 ppm (equal to 0, 0.48, 6.48 and 159.9 mg/kg bw per day for males and 0, 0.57, 7.68 and 189.5 mg/kg bw per day for females, respectively). There was no evidence of carcinogenicity. In males, changes at all doses consisted of cloudy eyes, corneal opacities, vascularization and keratitis in the clinical, ophthalmological and histopathological examinations, decreased body weights, hepatocyte fatty vacuolation in the liver and thyroid follicular cysts.

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

Mesotrione was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. There was no evidence of genotoxicity.

The Meeting concluded that mesotrione is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that mesotrione is unlikely to pose a carcinogenic risk to humans.

In a two-generation reproductive toxicity study in mice, animals were given diets containing mesotrione at a concentration of 0, 10, 50, 350, 1500 or 7000 ppm (equal to 0, 2.1, 10.2, 71.4, 311.8 and 1472 mg/kg bw per day for males and 0, 2.1, 10.0, 71.3, 301.6 and 1439 mg/kg bw per day for females, respectively). At the highest dose tested, F_1 adults and pups showed evidence of cataractous changes at clinical, gross and histopathological examination. Pups at the next lower dose also exhibited decreased body weight and body weight gain, clinical, gross and histopathological changes to the eyes (opaque/cloudy eyes, cataractous change) and increased plasma tyrosine levels. The NOAEL for parental toxicity was 1500 ppm (equal to 301.6 mg/kg bw per day). The NOAEL for reproductive toxicity was 7000 ppm (equal to 1439 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 350 ppm (equal to 71.3 mg/kg bw per day).

In a three-generation reproductive toxicity study in rats, animals were given diets containing mesotrione at a concentration of 0, 2.5, 10, 100 or 2500 ppm (equal to 0, 0.3, 1.1, 11.6 and 278.1 mg/kg bw per day for males and 0, 0.3, 1.1, 11.7 and 297.2 mg/kg bw per day for females, respectively), with an F_2 recovery group in which the dams were not treated through gestation. Effects in the parental generations consisted of ocular changes in clinical, ophthalmological, gross and histopathological examinations at dietary concentrations of 10 ppm and above, along with increased plasma tyrosine levels. In pups, cloudy/opaque eyes, keratitis and/or corneal vascularization were observed in all treated groups in males and at 100 and 2500 ppm in females in litters exposed to mesotrione in utero. Plasma tyrosine levels were measured in pups in the F_{3A} groups and were increased in all treatment groups in the continuous treatment animals; levels were comparable to those of controls in all the recovery groups. Decreased litter size, decreased survival, decreased percentage of pups born live and increased whole litter loss were observed at the highest dose tested.

A mode of action study in rats was performed to determine the link between tyrosinaemia and the changes noted in the rat reproductive toxicity study. In a modified one-generation reproductive toxicity study, animals were exposed to 0 ppm mesotrione with 0%, 0.5%, 1% or 2% tyrosine or to 2500 ppm mesotrione with 0%, 0.5%, 1% or 2% tyrosine from day 1 of gestation until termination on day 29 postpartum. Tyrosine and mesotrione increased plasma tyrosine levels and caused increases in whole litter losses, although the effect of mesotrione was greater than that of dietary tyrosine. The Meeting concluded that the reproductive effects observed in rats were likely a consequence of the elevated levels of tyrosine.

In a developmental toxicity study in mice, pregnant females were dosed at 0, 10, 60, 150 or 600 mg/kg bw per day. There were no signs of maternal or embryo/fetal toxicity up to 600 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rats, pregnant females were dosed at 0, 100, 300 or 1000 mg/kg bw per day. Maternal body weight and feed consumption were decreased at all doses. In fetuses, delays in ossification were increased at all doses.

In a developmental toxicity study in rabbits, pregnant females were dosed at 0, 100, 250 or 500 mg/kg bw per day. At 250 and 500 mg/kg bw per day, there were increases in abortions and decreased defecation. The NOAEL for maternal toxicity was 100 mg/kg bw per day, based on increased abortions and decreased defecation at 250 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 500 mg/kg bw per day, the highest dose tested.

An investigative study was performed with pregnant female rabbits treated as follows: control (no tyrosine or mesotrione), tyrosine (1% dietary), mesotrione (500 mg/kg bw per day by gavage) and tyrosine and mesotrione (1% dietary tyrosine and 500 mg mesotrione/kg bw per day by gavage). Plasma tyrosine levels were increased in all groups treated with mesotrione, tyrosine or a combination of the two. In groups treated with both mesotrione and tyrosine, the plasma tyrosine levels were highest, followed by mesotrione-only dams and, lastly, tyrosine-only treated dams. Likewise, delays in ossification were most prevalent in the fetuses of dams treated with both mesotrione and tyrosine, followed by mesotrione-only and tyrosine-only treated dams; however, delays were prevalent in all treated groups at rates higher than those in the concurrent controls. There was only one abortion, which occurred in the group treated with both mesotrione and tyrosine. As such, the Meeting concluded that delays in ossification were related to the increase in plasma tyrosine levels. There was insufficient information to enable a conclusion to be reached with regard to abortions.

The Meeting concluded that mesotrione is not teratogenic.

In an acute neurotoxicity study in rats, no neurotoxic effects were seen at the NOAEL of 2000 mg/kg bw, the highest dose tested.

In a 13-week dietary neurotoxicity study in rats, ophthalmoscopic findings were observed at 100 ppm (equal to 8.25 mg/kg bw per day). No neurotoxicity was observed up to 5000 ppm (equal to 402.80 mg/kg bw per day), the highest dose tested.

The Meeting concluded that mesotrione is not neurotoxic.

In a 4-week dietary immunotoxicity study in mice, no effects on immunoglobulin M response to sheep red blood cells or any other signs of immunotoxicity were observed at 5000 ppm (equal to 1364 mg/kg bw per day), the highest dose tested.

The Meeting concluded that mesotrione is not immunotoxic.

Toxicological data on metabolites and/or degradates

For MNBA, a plant and livestock metabolite, studies of metabolism, HPPD inhibition, acute toxicity, short-term toxicity and genotoxicity were performed.

When given to rats as a single oral dose of 75 mg/kg bw, [^{14}C]MNBA was minimally absorbed and excreted in the urine. The majority was converted to AMBA in the gut, which was excreted unabsorbed.

MNBA was a very weak inhibitor of HPPD compared with mesotrione.

MNBA is of low acute oral toxicity, with an LD_{50} of > 5000 mg/kg bw.

In a 28-day gavage study in rats, MNBA was given in corn oil at a dose of 0, 15, 150 or 1000 mg/kg bw per day. The NOAEL was 1000 mg/kg bw per day, the highest dose tested.

In a 90-day study in rats, animals were given MNBA in the diet at a concentration of 0, 100, 650 or 3000 ppm (equal to 0, 7.7, 50.6 and 231.0 mg/kg bw per day for males and 0, 8.8, 56.9 and 263.7 mg/kg bw per day for females, respectively). At 3000 ppm, body weights were decreased

statistically significantly (by 8%) in males, and triglycerides were increased (by 36%) in females. The NOAEL was 650 ppm (equal to 50.6 mg/kg bw per day), based on equivocal effects on body weight and increased triglycerides.

MNBA was tested in an adequate range of genotoxicity assays. No evidence of genotoxicity was observed.

For AMBA, a plant and livestock metabolite, studies of HPPD inhibition, acute toxicity and genotoxicity were performed.

AMBA was a very weak inhibitor of HPPD compared with mesotrione.

AMBA is of low acute oral toxicity, with an LD_{50} of > 5000 mg/kg bw.

AMBA showed no evidence of genotoxicity in a reverse mutation assay or in a mammalian cell cytogenetic assay in the presence of metabolic activation and gave positive results in the mammalian cell cytogenetic assay in the absence of metabolic activation.

As there was insufficient information to determine the toxicological profile of MNBA and AMBA, their toxicological relevance was assessed using JMPR's metabolite assessment scheme included in the guidance document for WHO monographers. On the basis of this assessment, the Meeting concluded that these metabolites are unlikely to be a safety concern.

Human data

In a study in which human volunteers were exposed to a single oral dose of mesotrione of 0.1, 0.5 or 4 mg/kg bw in capsules, there were no symptoms, clinical signs or changes on ophthalmological examination. In volunteers given 4 mg/kg bw, plasma tyrosine levels were increased up to 48 hours following dosing, with a peak tyrosine concentration of up to 420 nmol/mL plasma; unchanged mesotrione was found in the urine.

There are no reports of poisoning cases with mesotrione.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.5 mg/kg bw on the basis of the NOAEL of 350 ppm (equal to 49.7 mg/kg bw per day), based on decreased body weight, body weight gain and feed efficiency in male mice in an 18-month toxicity and carcinogenicity study. A safety factor of 100 was applied.

The Meeting considered the mode of action of the HPPD-dependent effects of mesotrione and concluded that the rat was not an appropriate model on which to base the toxicological evaluation.

The Meeting concluded that it was not necessary to establish an ARfD for mesotrione in view of its low acute oral toxicity and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of mesotrione

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and	Toxicity	350 ppm, equal to 49.7 mg/kg bw per day	7 000 ppm, equal to 897.7 mg/kg bw per

Species	Study	Effect	NOAEL	LOAEL
	carcinogenicity[a]			day
		Carcinogenicity	7 000 ppm, equal to 897.7 mg/kg bw per day[b]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	7 000 ppm, equal to 1 439 mg/kg bw per day[b]	–
		Parental toxicity	1 500 ppm, equal to 301.6 mg/kg bw per day	7 000 ppm, equal to 1439 mg/kg bw per day
		Offspring toxicity	350 ppm, equal to 71.3 mg/kg bw per day	1 500 ppm, equal to 301.6 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	600 mg/kg bw per day[b]	–
		Embryo and fetal toxicity	600 mg/kg bw per day[b]	–
Rat	Two-year study of toxicity and carcinogenicity[a]	Carcinogenicity	159.9 mg/kg bw per day[b]	–
Rabbit	Developmental toxicity study[c]	Maternal toxicity	100 mg/kg bw per day	250 mg/kg bw per day
		Embryo and fetal toxicity	500 mg/kg bw per day[b]	—
Dog	One-year study of toxicity[d]	Toxicity	100 mg/kg bw per day	600 mg/kg bw per day

[a] Dietary administration.
[b] Highest dose tested.
[c] Gavage administration.
[d] Capsule administration.

Estimate of acceptable daily intake (ADI)

0–0.5 mg/kg bw

Estimate of acute reference dose (ARfD)

Unnecessary

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 mesotrione

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; extensive (> 60%)
Dermal absorption	No data
Distribution	Rapidly eliminated; highest residues in carcass, gastrointestinal tract, liver and kidneys

Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Largely complete within 24 hours; primarily via urine (41–70% in mice and 54–84% in rats), with 21–38% in faeces
Metabolism in animals	Mostly excreted unchanged
Toxicologically significant compounds in animals and plants	Mesotrione, MNBA and AMBA
Acute toxicity	
Rat, LD_{50}, oral	> 5 000 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.75 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Mildly irritating
Guinea-pig, dermal sensitization	Not sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Body weight
Lowest relevant oral NOAEL	100 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day (rabbit)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Body weight
Lowest relevant oral NOAEL	49.7 mg/kg bw per day (mouse)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans
Genotoxicity	
	Unlikely to be genotoxic
Reproductive toxicity	
Target/critical effect	Decreased body weight, clinical, gross and histopathological changes to the eye
Lowest relevant parental NOAEL	301.6 mg/kg bw per day (mouse)
Lowest relevant offspring NOAEL	71.3 mg/kg bw per day (mouse)
Lowest relevant reproductive NOAEL	1 439.1 mg/kg bw per day (mouse)
Developmental toxicity	
Target/critical effect	Abortions and decreased faecal output
Lowest relevant maternal NOAEL	100 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	500 mg/kg bw per day, highest dose tested (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested
Subchronic neurotoxicity NOAEL	402.80 mg/kg bw per day, highest dose tested
Developmental neurotoxicity NOAEL	No data

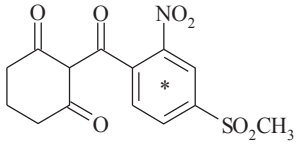
Other toxicological studies	
Studies on toxicologically relevant metabolites	MNBA:
	Metabolism: Minimally absorbed, excreted primarily in urine, majority in gut at 12 hours converted to AMBA
	HPPD inhibition: very weak compared with mesotrione
	Oral LD_{50}: > 5 000 mg/kg bw
	NOAEL: 1 000 mg/kg bw per day, highest dose tested (4-week gavage study in rats)
	NOAEL: 50.6 mg/kg bw per day, based on equivocal decreases in body weights and increased triglycerides (90-day study in rats)
	Unlikely to be genotoxic
	AMBA:
	HPPD inhibition: very weak compared with mesotrione
	Oral LD_{50}: > 5 000 mg/kg bw
	Unlikely to be genotoxic
Medical data	
	No studies submitted

Summary

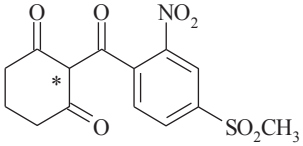
	Value	Study	Safety factor
ADI	0–0.5 mg/kg bw	Eighteen-month study of toxicity and carcinogenicity (mouse)	100
ARfD	Unnecessary	–	–

RESIDUE AND ANALYTICAL ASPECTS

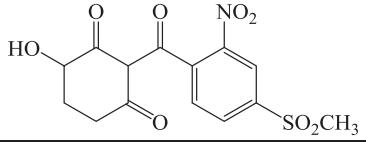
Mesotrione is a systemic pre-emergence and post-emergence herbicide for the selective contact and residual control of broadleaf weeds. The compound was scheduled for evaluation by 2014 JMPR as a new compound at the Forty-fifth Session of the CCPR (2013). Metabolism studies on animal and plants, confined rotational crops and environmental fate studies, analytical methods and residue trials on berries, okra, sweet corn, soya bean, asparagus, rhubarb maize, millet, oat, rice, sorghum, sugarcane and linseed were submitted for evaluation. The structure of mesotrione and the main metabolites found in livestock, plant tissues and soil are shown below

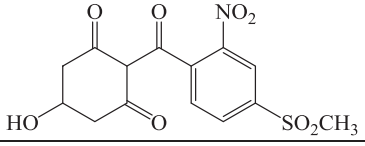


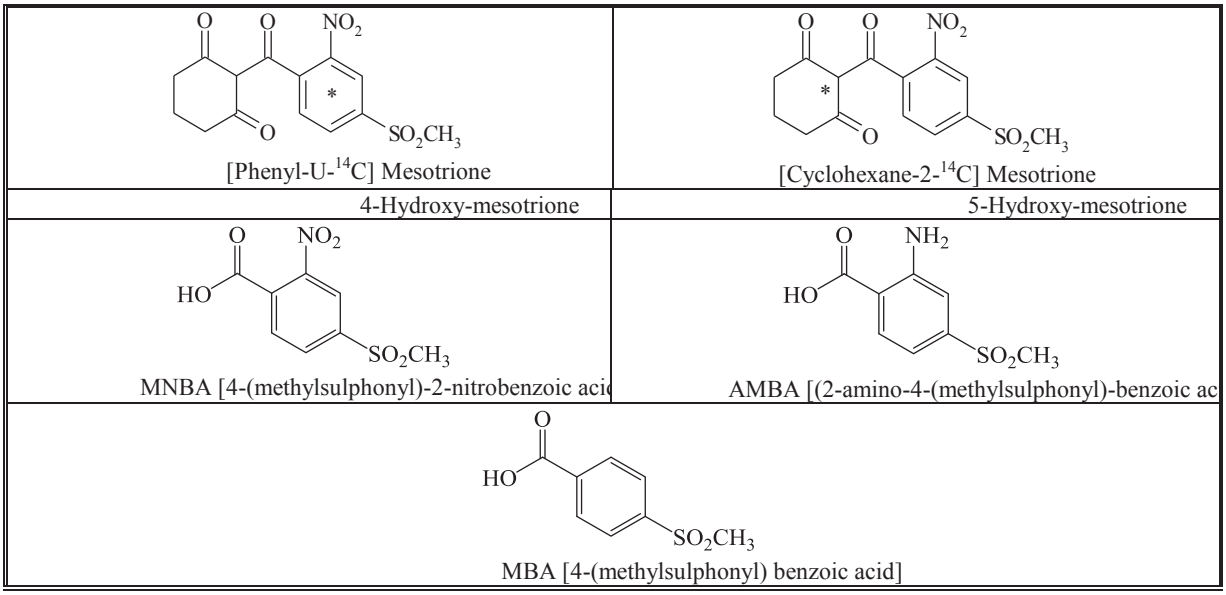
[Phenyl-U-^{14}C] Mesotrione



[Cyclohexane-2-^{14}C] Mesotrione







Animal metabolism

Rats

The metabolism of mesotrione was evaluated at the present Meeting by the JMPR WHO Panel. The compound is rapidly and extensively absorbed, minimally metabolized and excreted primarily in urine after a single or repeated dose. The majority of the radioactivity was excreted as the parent compound within 12 hours post-dose, accounting for 43–64% of the dose in urine. The metabolites found in the excreta includes 4 and 5-hydroxy mesotrione, MNBA and AMBA.

Livestock animals

Metabolism studies with mesotrione were conducted in lactating cows, swine and poultry. Additionally, the metabolism of AMBA was investigated in the cow.

In two metabolism studies conducted in lactating cows, the animals were dosed with [phenyl-U-^{14}C-]-mesotrione or [cyclohexane-2-^{14}C]-mesotrione for 7 consecutive days at a nominal rate of 10 ppm in the diet, and sacrificed 16 hours after the final dose. Over 90% of the administered dose was found in excreta, mostly in faeces. TRR was higher in liver and kidney (0.07 to 0.11 mg eq./kg), reached 0.007 mg eq./kg in muscle, 0.013 mg/kg eq in fat and 0.08 mg eq./kg in milk (at least 90% TRR in skimmed milk). Mesotrione accounted for 10–18% TRR in liver and kidney (0.01–0.02 mg eq./kg). AMBA was identified in kidney of the phenyl label experiment (0.01 mg eq./kg).

One female swine was dosed orally with [phenyl-U-^{14}C]-mesotrione for 5 consecutive days at 6 ppm, and sacrificed 23 hours after the final dose. About 90% of the administered dose was recovered in the excreta, mostly in the faeces. Highest TRRs were found in liver (1.75 mg eq./kg) and kidney (0.12 mg eq./kg), with 0.01 mg eq./kg in muscle and 0.006 mg eq./kg in fat. Mesotrione was the main identified residues (90% TRR in liver, 73% TRR in kidney and 78% TRR in muscle). AMBA accounted for up to 2% TRR in tissues (up to 0.029 mg eq./kg in liver). MNBA was only detected in liver (0.005 mg eq./kg).

Two metabolism studies were conducted in poultry, in which hens were dosed for 10 consecutive days at 11 ppm either with [phenyl-U-^{14}C]-mesotrione or [cyclohexane-2-^{14}C]-mesotrione; the hens were sacrificed 16 hours after the final dose. The radioactivity in excreta accounted for over 90% of the administered dose, and contained mesotrione (up to 55% TRR) and AMBA (18% TRR). TRRs were similar in both experiments for liver (1.1–1.2 mg eq./kg) and kidney

(0.06–0.07 mg eq./kg), but were higher in the cyclohexane experiment in muscle (up to 0.012 mg/kg eq), fat (up to 0.048 mg eq./kg), reaching 0.094 mg eq./kg in egg yolk, and 0.025 mg eq./kg in the white. Mesotrione was not detected in muscle in any experiment, and was the only compound identified in tissues and eggs in both experiments, corresponding to at least 70% TRR in the liver and fat. In egg yolk, mesotrione accounted for 81% TRR in the phenyl experiment, and 19.5% TRR in the cyclohexane experiment, in which about 15% TRR was shown to be incorporated into palmitic/oleic acid.

A lactating cow received [phenyl-U-^{14}C]-AMBA for 7 days at 12.2 ppm in the diet and was sacrificed 23 hours after the final dose. About 90% of the dose was recovered in the excreta, mostly in the faeces. Highest residues were found in kidney (0.053 mg eq./kg), with AMBA accounting for 79% TRR. Perineal fat contained 0.018 mg eq./kg, 62% identified as AMBA. TRR in liver were 0.005 mg eq./kg, and reached a maximum of 0.009 mg eq./kg in milk (day 6), but were not characterized. No radioactive residues were detected in muscle.

In summary, the biotransformation of mesotrione in livestock involves the oxidative cleavage of the parent molecule to yield MNBA, which is reduced in the nitro group to give AMBA. Highest residues were found in liver and kidney, and the levels in muscle were low, reaching a maximum of 0.012 mg eq./kg Mesotrione accounted for up to 18% TRR in cow liver and kidney, at least 70% TRR in tissues of swine and poultry, and up to 80% TRR in egg yolk. No single compound was detected in muscle. The metabolism of Mesotrione in rats was found to be similar to that described for livestock.

Plant metabolism

Metabolism studies were conducted in cranberries, tolerant soya bean, maize, rice and peanuts. [Phenyl-U-^{14}C]-mesotrione was applied twice to cranberry plants at 0.331 + 0.242 kg ai/ha (1×) or 0.919 + 0.642 kg ai/ha (3× rate), and samples harvested 46 days after the last treatment (DAT). TRRs in mature foliage were 16.8 mg eq./kg and 31.8 mg eq./kg for 1× and 3×, respectively. TRRs in the mature cranberry fruit were 2.6 mg eq./kg and 4.9 mg eq./kg, respectively, mostly as mesotrione (60–67% TRR) and AMBA (24–35% TRR); MNBA accounted to up to 3%TRR.

Mesotrione tolerant soya bean seeds grown in sandy loam soil were treated with either [phenyl-U-^{14}C]- or [cyclohexane-2-^{14}C]-mesotrione using three GAP application regimes: one pre-emergence at 0.225 kg ai/ha (T1), a combined pre-emergence at 0.225 kg ai/ha followed by a post-emergence at 0.125 kg ai/ha (T2), or one post-emergence at 0.225 kg ai/ha (T3). Forage was sampled at 22–28 DAT, hay at 40–42 DAT and seeds at 90–123 DAT.

Higher radioactivity was recovered from the phenyl label experiment. In forage, TRR were 0.16 to 0.5 mg eq./kg, mostly as MNBA (13 to 24% TRR; 0.04 to 0.06 mg eq./kg); mesotrione and its 4 and 5-hydroxy metabolite accounted for up to 14.6% TRR each (0.01 to 0.08 mg eq./kg). In hay, TRR ranged from 0.14 mg/kg eq (T1) to 2 mg eq./kg (T2), mostly MNBA (up to 20% TRR) and 4/5-hydroxy-mesotrione (up to 16% TRR); mesotrione accounted for up to 9% TRR. AMBA was only detected in T2 hay (0.055 mg eq./kg; 2.7% TRR). Residues in soya bean seed ranged from 0.052 to 0.104 mg eq./kg, with mesotrione and 4/5-hydroxy-mesotrione the main compounds identified (< 10% TRR). Low levels of MNBA and AMBA were found in the T1 and T2 samples (< 5% TRR, 0.005 mg eq./kg).

Results from the cyclohexane experiment showed mesotrione accounting for up to 18% TRR in forage, 8.2% TRR in hay and 5.1% TRR in seed (0.02 mg eq./kg). 4 and 5-hydroxy-mesotrione accounted for up to 19% TRR in forage and hay, and 7% TRR in seeds.

Three studies were conducted with maize, two with [phenyl-U-^{14}C]-mesotrione and/or one with [cyclohexane-2-^{14}C]–mesotrione. In all cases, the compound was applied to the soil surface after planting the seeds at a rate of 0.3 kg ai/ha (pre-emergence; T1) or post-emergence at 0.16–0.18 kg ai/ha, 28 days after planting (T2).

Results from the phenyl label experiments showed higher total residues in fodder/stover (0.8 to 1.1 mg eq./kg) and forage (0.244 to 0.356 mg eq./kg). Over 60% of the residues in fodder were not extracted with ACN/water. In T1 forage, MNBA and AMBA were the major residues (up to 19.7 and 12.2% TRR, respectively). In fodder, AMBA was the major residue (up to 28% TRR in T2). 4-hydroxy-mesotrione was mainly present in forage (up to 8% TRR, about 50% conjugated). Mesotrione was a minor component of the residues in all cases, present at a higher level in T1 forage samples (2.2% TRR, 0.008 mg eq./kg). TRR in grain were 0.01mg/kg eq, and were not further characterized.

In the cyclohexane experiment, TRR reached 0.1 mg eq./kg in forage and 0.33 mg eq./kg in fodder. In forage, the identified residues were mesotrione (up to 3% TRR) and 4-hydroxy-mesotrione (up to 10% TRR). About 18% TRR was incorporated into lignin and cellulose. Residues in grain were low (up to 0.011 mg eq./kg) and were not be further characterized.

Rice plants were treated at the 2–3 leaf stage with [phenyl-U-^{14}C]-mesotrione added directly to the paddy water at either 0.09 kg ai/ha (1×) or 0.225 kg ai/ha (2.5×). TRRs were higher in whole tops and straw (0.03 to 0.06 mg eq./kg at 1×), with 60–71% extracted by ACN/water. Residues in grain and husk (109 DAT) reached 0.01 mg eq./kg, up to 33% being extracted (acid released up to 75.1% TRR in grain). Immature whole tops from 1x rate contained mesotrione and 5-hydroxy-mesotrione at up to 0.01 mg eq./kg each (11 to 15% TRR), and traces of MNBA and AMBA (< 5% TRR from 1×). In 1× stalk and straw, mesotrione and its metabolites represented < 10% TRR each. No characterization was performed in grain. Residues from 2.5× samples were 2–5 times higher (0.02 mg eq./kg in grain).

[Phenyl-U-^{14}C] or [cyclohexane-2-^{14}C]-mesotrione were applied to the soil surface after planting peanut seed (pre-emergence) at 0.3 (T1) or 0.8 kg ai/ha (T2). Peanut foliage was harvested 90 DAT (50% maturity), mature peanuts and peanut hay at 153 DAT. Residues from [phenyl-U-^{14}C] treatment were higher in foliage (0.028 and 0.064 mg eq./kg, in T1 and T2, respectively) and up to~ 0.01 mg eq./kg in hay, hull and nutmeat. Traces of MNBA, MBA, AMBA and 4-hydroxy-misotrione were found in hay (<6% TRR, ≤ 0.002 mg eq./kg), but only AMBA was found in nutmeat (up to 15% TRR, 0.002 mg eq./kg, in T1). TRR from [cyclohexane-2-^{14}C] treatment were ≤0.01 mg eq./kg in T1 samples and ranged from 0.01 and 0.02 mg eq./kg in T2. 4-hydroxy-mesotrione was only identified in hulls (7% TRR). The peanut oil fraction was shown to be composed primarily of ^{14}C-labelled neutral lipids.

In summary, the metabolic pathway of mesotrione following pre- and/or post-emergence foliar applications in cranberries, maize, rice, peanut and tolerant soya bean are similar. It proceeds via cleavage of the parent molecule to yield MNBA and reduction to AMBA, which either conjugated or degraded to MBA. Mesotrione is also hydroxylated in the cyclohexane-dione ring to give 4 or 5-hydroxy-mesotrione. Incorporation of radioactive residues into natural products (lignin cellulose sugar or lipid) was seen in all crops, except cranberry fruit. Residues in cranberry fruits were mostly mesotrione and AMBA (over 20% TRR each). Maize, soya and rice feed commodities contained mostly MNBA and AMBA (> 10% TRR in most cases). Residues in grains were low and mesotrione only represented higher than 10% TRR in tolerant soya bean seed.

Environment fate

The photolysis of [phenyl-^{14}C] mesotrione and [cyclohexane-^{l4}C]-mesotrione was studied in silt loam soil treated at 0.3 kg ai/ha and incubated in local sunlight (latitude 37° 56') at 20 to 24°C. About half of the radioactivity was present as mesotrione at 12–13 DAT. MNBA and AMBA accounted for 2-8% TRR at 5 DAT, increasing up to 8% TRR at 30 DAT.

The metabolism of [phenyl-2-^{14}C] or [cyclohexane-^{l4}C]-mesotrione applied to various soils at rates ranging from 0.165 to 0.85 kg ai/ha and kept under aerobic conditions in the dark at 25±1°C for 28 to 60 days was investigated. Mesotrione degrades relatively fast, with DT_{50} values ranging from 4.5 to 32 days. DT_{50} for MNBA was < 2 days in these studies.

In two water sediment systems experiments conducted with either [phenyl-2-^{14}C] or [cyclohexane-^{l4}C]-mesotrione at 0.20 kg ai/ha and incubated in the dark for 101 days, showed DT_{50} were from 3 to 6 days, with mesotrione in the sediment never exceeding 4% AR. MNBA and AMBA were found in both water and sediment, starting at day 3.

The aerobic degradation of [phenyl-2-^{14}C]-AMBA was studied in soils incubated up to 60 days in the dark, showing DT_{50} ranging from 2 to 6 days.

Field studies

In six studies conducted with soils collected from different regions of Europe, mesotrione was applied at 0.15–0.2 kg ai/ha. MNBA and AMBA were detected at 6 DAT in 0–10 cm horizon (0.031 and 0.006 mg eq./kg, respectively). No residues of mesotrione or metabolites were detected in the soil below 10 cm. DT_{50} ranged from 2 to 8 days.

In one study conducted with four soils from England and USA treated with MNBA at 0.22 kg ai/ha, DT_{50} ranged from 0.6 to 10.6 days.

Confined rotational crops

Endive, radish and wheat were sown 120 days after a sandy loam soil being treated with [phenyl-U-^{14}C] or [cyclohexane-2-^{14}C]-mesotrione at 0.165 kg ai/ha. Endive was harvested at 78–63 days after planting (DAP), radish roots and leaves at 56 DAP, wheat forage at 22 DAP, wheat hay at 57 DAP and wheat grain and straw at 134–131 DAP. In the [phenyl-U-^{14}C] experiment, residues in soil declined to 34% of the applied radioactivity (AR) at 120 DAT, with the most abundant metabolites being MNBA (8% AR) and AMBA (2% AR); mesotrione accounted for only 0.1% AR. TRR were 0.02 to 0.04 mg eq./kg in wheat forage, hay and straw, mostly MNBA (0.011 mg eq./kg in forage). Residues were 0.006 mg eq./kg in wheat grain, 0.014 mg eq./kg in endive and 0.004 mg eq./kg in radish root and leaves. TRR in all cyclohexane-2-^{14}C samples were < 0.005 mg eq./kg in endive, and wheat straw, and were not further characterized.

[Phenyl-U-^{14}C] or [cyclohexane-2-^{14}C]-mesotrione was applied at 0.308 kg ai/ha (T1, characteristic of pre-emergence) and 0.462 kg ai/ha (T2, characteristic of pre + post-emergence) onto a sandy loam soil, and wheat, soya, endive or radish planted at 30, 120 and/or 300 DAT. Residues in soil declined to 27% AR at 300 DAT. Residues in wheat commodities from the [phenyl-U-^{14}C] experiment were higher in straw (2.58 mg eq./kg at 30 DAT, T1). In wheat grain, residues were 0.038 mg eq./kg at 30 DAT (T1) and 0.014–0.015 mg eq./kg at 120 and 300 DAT (T2). At 30 DAT (T1), the major identified metabolite was MNBA, with residues ranging from 0.17 to 0.63 mg eq./kg in wheat forage, hay and straw and 0.003 mg eq./kg in grain. AMBA was mostly present as sulphate conjugate (total of 0.67 mg eq./kg in straw), and mesotrione and its 4-OH metabolite were only detected in forage (0.01 mg eq./kg).

At 30 DAT (T1), residues were 0.145 mg eq./kg in soya bean, and 0.46–0.64 mg eq./kg in soya feed. MNBA was 0.17–0.31 mg eq./kg in soya forage and hay and 0.014 mg eq./kg in soya bean. AMBA levels were 0.02-0.07 mg eq./kg Residues in endive and radish ranged from 0.037 to 0.053 mg eq./kg at 120 DAT, declining to 0.005 to 0.019 mg eq./kg at 300 DAT (T2). The major residue was MNBA (0.02 mg eq./kg at 120 DAT, T2, in endive and radish tops).

Highest residues from [cyclohexane-2-^{14}C] experiment were found at 30 DAT, T1: 0.05 - 0.06 mg eq./kg in wheat feed, 0.01 mg eq./kg in wheat grain, and 0.02–0.03 mg eq./kg in soya bean samples. Residues in endive and radish were < 0.01 mg eq./kg Mesotrione and 4-hydroxy mesotrione were identified in wheat and soya bean feed (< 0.01 mg eq./kg, at 30 DAT, T1).

In summary, mesotrione degrades quickly in soil under aerobic conditions. Although mesotrione is relatively stable to hydrolysis at pH 5–9 (less than 10% degradation after 30 days at 25 °C), it degrades rapidly in flooded systems with a half-life of approximately 4 days. Mesotrione metabolites, mainly MNBA, are expected in wheat and soya bean feed, endive and radish root when

the crops are planted up to 120 days after the soil is treated with mesotrione at 0.3 kg ai/ha rate or higher. As currently the compound is used at rates lower than 0.3 kg ai/ha, no residues arriving from the use of mesotrione are expected in rotational crops.

Methods of analysis

Mesotrione residues in vegetable crops may be analysed by LC-MS/MS (negative mode, m/z=338 → 291) after extraction with acetonitrile/water and cleaned up by SPE. Recovery data for mesotrione in maize commodities and cranberries showed good performance (84–114% recovery, 3–21% RSD, n=3–6) at the 0.01 mg/kg (LOQ) to 10 mg/kg range. The method was used in various supervised trials, with recovery data for mesotrione and MNBA within the acceptable levels at the LOQ or higher.

A modified QuEChERS LC-MS/MS multi-residue method (no clean up with primary-secondary amine (PSA) is used) was validated for mesotrione in oranges, maize and oilseed rape, with a LOQ of 0.01 mg/kg.

In a reversed-phase HPLC-fluorescence method, mesotrione and MNBA residues are extracted with acetonitrile:water (1:1) and cleaned up on silica SPE. The extract is submitted to reversed phase HPLC, the mesotrione fraction converted to MNBA with H2O2 and reduced to AMBA using acidic SnCl2 and the MNBA fraction reduced to AMBA. Each fraction is cleaned-up by C18 SPE, and the AMBA conversion product quantified by HPLC-fluorescence. The method was validated for corn commodities with a LOQ of 0.01 mg/kg.

In a GC-MS method, mesotrione and MNBA residues are extracted from corn commodities with acetonitrile:water (1:1), acidified, partitioned with methylene chloride, which is evaporated and the residue heated with Jones Reagent (Cr^{VI} oxide acid solution) to oxidize mesotrione to MNBA. The total MNBA is extracted with ethyl acetate, evaporated to dryness, and the residue reacted with 2-iodopropane and potassium carbonate to form isopropyl ester of MNBA for analyse by GC-MS. The method determines both mesotrione and MNBA at a combined LOQ of 0.01 mg/kg.

The acetonitrile:water (1:1) extraction efficiency was radio-validated using incurred radioactive residues in forage. After extraction using a high speed homogeniser, an aliquot was partitioned three times into ethyl acetate, and residues of mesotrione and MNBA quantified by TLC with storage-phosphor autoradiography. Levels of mesotrione and MNBA in forage were similar to the results obtained after exhaustive extraction within the metabolism study.

Mesotrione and MNBA residues are extracted from milk and eggs with acetone and from animal tissues with acetone: water, the extract acidified, partitioned into methylene chloride, and residues of mesotrione oxidised to MNBA using H_2O_2. MNBA is reduced with acidic $SnCl_2$ and AMBA determined by reversed phase HPLC-fluorescence detection. The LOQ was 0.01 mg/kg in all matrices. Mesotrione may also be determined in animal matrices using the modified QuEChERS, excluding PSA, at an LOQ of 0.01 mg/kg.

The analytical methods were considered fit for purpose to determine mesotrione alone or in combination with MNBA in plant and animal commodities at a LOQ of 0.01 mg/kg.

Stability under frozen conditions

Residues of mesotrione and/or MNBA in fortified samples of maize commodities, radish root, and soya bean seed at 0.1 mg/kg were stable under frozen conditions for at least 32 months (at least 80% of the residues remained, quantified as AMBA by HPLC-FL). Samples of blueberry, asparagus, sugarcane and okra fortified with mesotrione at 1.0 mg/kg were shown to be stable for at least 13 months when stored frozen (quantified by HPLC-MS/MS). The residue trials reports also include additional information on storage stability, and the samples were stored within the period that guaranteed the integrity of the residues at the time of analysis.

Definition of the residue

Metabolism studies conducted in cow, swine and poultry fed with ^{14}C mesotrione at 6 to 11 ppm showed higher residues in liver and kidney, and ranged from 0.01 to 0.08 mg eq./kg in muscle, milk and eggs. When detected, mesotrione was the main residue found in animal commodities, accounting for up to 18% TRR in cow liver and kidney, at least 70% TRR in tissues of swine and poultry, and up to 80% TRR in egg white. When cow was fed with ^{14}C AMBA, residues reached a maximum of 0.05 mg eq./kg in kidney and fat, with over 60% as AMBA. Residues in other tissues and in milk were < 0.01 mg eq./kg

The Meeting agreed that the residue definition of mesotrione in animal commodities for enforcement and dietary exposure assessment is mesotrione.

The residues do not concentrate in fat and mesotrione has a log P_{ow} of 0.1, confirming that mesotrione is not fat soluble.

Mesotrione is a herbicide that can be applied to the soil pre and/or post emergence of the plant, with exception of cranberry, for which the use is foliar. The compound is rapidly degraded in soil. Metabolism study showed residues in cranberry fruits mostly as mesotrione (over 60% TRR) and AMBA (over 20% TRR). Metabolism studies conducted in tolerant soya bean, maize, rice and peanut showed higher residues in feed commodities, mostly as mesotrione (up to 28% TRR in rice tops), MNBA (up to 24% TRR in soya bean forage) and AMBA (up to 29% TRR in maize fodder). Total residues in edible commodities were low (≤ 0.03 mg eq./kg) and when characterized, showed mesotrione as the main residue.

The Meeting concluded that MNBA and AMBA appear to be of low toxicological concern. When the information was available, MNBA was not detected in any sample from the residue trials.

The Meeting agreed that mesotrione is an adequate marker for the uses of mesotrione in plants and is suitable for dietary intake assessment

The Meeting agreed in the following residue definition for both plant and animal commodities for enforcement and dietary risk assessment: *Mesotrione*

The residues are not fat soluble.

Residues of supervised residue trials on crops

Cranberry

GAP in USA for cranberries is 2 broadcast foliar applications at 0.28 kg ai/ha, PHI 45 days. In five trials using 2 applications, the first being at 0.388 kg ai/ha, residues were: < 0.01 mg/kg (5), indicating that no residues are expected when the product is applied at the GAP rate.

The Meeting agreed to recommend a maximum residue level of 0.01* mg/kg, and a STMR of 0 mg/kg for mesotrione in cranberries

Bush berries and cane berries

GAP in USA for bush and cane berries is 1 post-direct spray at 0.21 kg ai/ha pre-emergence (before bloom), with no PHI specified.

In one trial conducted in blueberry in USA according to GAP (application at BBCH 59), residues were < 0.01 mg/kg (77 DAT). In five other trials where the application was done after bloom residues at 32 to 88 DAT were < 0.01 mg/kg.

In four trials conducted with raspberry at GAP, residues at 32 to 88 DAT where < 0.01 mg/kg (4) at 52 to 83 DAT.

As no residues above the LOQ were found even in the late application trials, the Meeting agreed to estimate a maximum residue level of 0.01* mg/kg and a STMR of 0 mg/kg for bush berries and cane berries

Okra

In USA, mesotrione can be applied either at pre-emergence (0.21 kg ai/ha) or post emergence (0.105 kg ai/ha). PHI in both cases is 28 days. Five post-emergence trials conducted according to GAP gave residues < 0.01 mg/kg (5).

The Meeting agreed to recommend a maximum residue level of 0.01* mg/kg, and a STMR of 0.01 mg/kg for mesotrione in okra.

Sweet corn

Mesotrione is registered in Germany for post-emergence use on sweet-corn (BBCH 12–18) at 0.15 kg ai/ha. In four trials conducted in France at this GAP rate gave residues were: < 0.01 mg/kg (4) in the kernels and in the cob at 38 to 61 DAT.

In USA, mesotrione can be used in sweet corn via three application regimes: 1) one pre-emergence application at 0.27 kg ai/ha, 2) two post emergence applications, with a maximum of 0.21 kg ai/ha; or 3) 1× pre + 1× post emergence, with a maximum of 0.27 kg ai/ha. In all cases, the PHI is 45 days. The second application should be done up to the 8 leaf stage. In one trial, conducted according to regime 2, residues in the ears were: < 0.01 mg/kg (2); other two trials conducted at the same rate residue were the same 28 to 32 DAT. In 12 trials conducted a higher rate (0.48 to 0.50 kg ai/ha; regimes 1 or 2 residues were: < 0.01 mg/kg from 23 to 36 DAT.

Although only one trial was conducted in USA according to GAP, 14 trials conducted at higher rate and/or lower PHI showed that no residues are expected in the ears of sweet corn after treatment according to GAP.

The Meeting agreed to estimate a maximum residue level of 0.01* mg/kg and a STMR of 0 mg/kg for mesotrione in sweet corn (kernels plus cob without husk).

Soya bean, dry

In USA, GAP for mesotrione in conventional soya is one pre-emergence application at 0.21 kg ai/ha, with no PHI specified. In twenty trials conducted according to GAP, residues at 117 to 174 DAT were < 0.01 mg/kg (20). Three trials conducted at higher rates (0.6–1 kg ai/ha) gave the same results.

GAPs for mesotrione tolerant soya are 1) one pre-emergence or 2) early post-mergence (up to BBCH 13) application at 0.225 kg ai/ha, or 3) one pre + one post emergence application (BBCH 14–60) at 0.225 kg ai/ha and 0.125 kg ai/ha, respectively. Forty seven trials were conducted with tolerant soya using application using regimes 2 or 3, residues in the mature seeds were: < 0.01 (24) and 0.02 (3) mg/kg.

Using the data from trials conducted in tolerant crops, the Meeting agreed to estimate a maximum residue level of 0.03 mg/kg and a STMR of 0.01 mg/kg for mesotrione in soya bean, dry.

Asparagus

In the USA, mesotrione can be use in asparagus either as a pre-emergence application on the soil surface at 0.27 kg ai/ha in the spring prior to spear emergence, one application after completion of harvesting directed to the weed at 0.105 kg ai/ha, or both at a maximum of 0.27 kg ai/ha. In eight trials conducted in USA using the pre-emergence GAP, residues at 8 to 18 DAT were < 0.01 mg/kg (8). In 16 other trials the application was done after emergence of the plant.

The Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0.01 mg/kg for mesotrione in asparagus.

Rhubarb

In USA, mesotrione can be use in rhubarb as pre-emergence application on the soil surface prior to any spring green-up at 0.21 kg ai/ha and 21 days PHI. In four trials conducted at GAP rate, residues at 28 to 42 DAT were <0.01 mg/kg. Four trials conducted at higher rate gave the same results.

As the PHI is not relevant to a pre-emergence application, the Meeting agreed to estimate maximum residue level of 0.01* mg/kg and a STMR of 0.01 mg/kg for mesotrione in rhubarb.

Maize

Mesotrione is registered in Germany for post-emergence use on maize (BBCH 12–18) at 0.15 kg ai/ha. In two trials conducted in Germany and UK at this GAP gave results at 112 to 143 DAT of < 0.01 mg/kg (2).

In the USA, mesotrione can be used in maize in three application regimes: 1) one pre-emergence at 0.27 kg ai/ha, 2) two post emergence, with a maximum of 0.21 kg ai/ha; or 3) 1× pre + 1× post emergence, with a maximum of 0.27 kg ai/ha. The second application should be done up to the 8 leaf stage. In all cases, the PHI was 45 days. Eight trials were conducted in Canada and the USA using regime 1 and 32 trials using regime 3 at rates higher than USA GAP. Grain harvested at 68 to 145 DAT gave residues <0.01 mg/kg.

The results from North American trials conducted at higher rate show that no residues are expected in maize grain after treatment according to GAP.

The Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0 mg/kg for mesotrione in maize grain.

Millet

Mesotrione is registered in the USA as one pre-emergence use at 0.21 kg ai/ha, and no PHI specified. In five trials conducted according to GAP residues were: < 0.01 mg/kg (5) in millet grain (84 to 132 DAT).

With the support from the data from other cereals, the Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0 mg/kg for mesotrione in millet grain.

Oat

Mesotrione is registered in USA either as one pre-emergence use at 0.21 kg ai/ha or as a post-emergence application at 0.105 kg ai/ha. PHI is 50 days. In sixteen post-emergence trials conducted at GAP, residues in oat grain were < 0.01 mg/kg (16). Two trials conducted at up to 5 times the rate gave the same results.

The Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0 mg/kg for mesotrione in oat grain.

Rice

Mesotrione is registered in paddy rice in Republic of Korea as post-planting into the water (5–7 days after transplanting) at 1×0.09 kg ai/ha and no PHI specified. Ten trials were conducted in Republic of Korea and Japan using either a single application at higher rate, two applications at the GAP rate and/or applying latter in the season. In all cases, residues at 45 to 140 DAT were < 0.01 mg/kg.

Although the trials were not according to GAP, these results indicate that no mesotrione residues are expected when the product is used according to GAP.

The Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0 mg/kg for mesotrione in rice grain, husked.

Sorghum

The registered use for mesotrione in sorghum in the USA is one pre-emergence application at 0.224 kg ai/ha up to 21 days before planting. In nine trials conducted according to GAP, residues at 78 to 134 DAT were < 0.01 mg/kg (9). Twelve post-emergence trials gave the same results.

The Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0 mg/kg for mesotrione in sorghum.

Sugar cane

The GAP for mesotrione in sugarcane in the USA is either two post-emergence applications at 0.10 kg ai/ha to the base of the sugar cane or a combination of one pre- and one post-emergence application not exceeding a total rate of 0.36 kg ai/ha. PHI is 114 days. In twenty four trials conducted according to either of the GAPs in USA gave residues of < 0.01 mg/kg (24) from 30 to 118 DAT. Two trials conducted at 3 or 5× the rate gave the same results within 114 days PHI.

In South Africa, GAP is a single early post-emergence at 0.15 kg ai/ha, and 181 days PHI. In four trials conducted at higher rate no residues were detected.

The Meeting agreed to estimate a maximum residue level of 0.01*mg/kg and a STMR of 0 mg/kg for mesotrione in sugar cane.

Linseed

Mesotrione is registered in the USA for linseed at one pre or one post-emergence application at 0.21 kg ai/ha, and no PHI specified. Five pre-emergence trials conducted according to GAP gave residues of < 0.01 mg/kg (5). Two post emergence trials conducted at a higher rate gave the same result.

The Meeting agreed to estimate a maximum residue level of 0.01* mg/kg and a STMR of 0.01 mg/kg for mesotrione in linseed.

Animal feed

Forage

Mesotrione is registered in Germany for post-emergence use on maize (BBCH 12–18) at 0.15 kg ai/ha, and no PHI specified. In three trials conducted in maize in France, Germany and UK matching German GAP, residues in stover (remaining plant) at 41-47 DAT were 0.01 mg/kg (3).

In the USA, mesotrione can be used in maize under three application regimes: 1) one pre-emergence at 0.27 kg ai/ha; 2) two post emergence, with a maximum of 0.21 kg ai/ha; or 3) 1× pre + 1× post emergence, with a maximum of 0.27 kg ai/ha. In all cases, PHI was 45 days for forage and stover. The second application should be made up to the 8 leaf stage (or BBCH 19).

In one trial conducted in USA according to GAP, residues in maize forage were 0.12 mg/kg.

Mesotrione is registered in USA in millet as one pre-emergence use at 0.21 kg ai/ha. In five trials conducted at GAP, residues in forage were < 0.01 mg/kg(5)

The Meeting estimated a median residue and a highest residue of 0.01 mg/kg for mesotrione in millet forage

Mesotrione is registered in oats in USA either as one pre-emergence use at 0.21 kg ai/ha or as post-emergence application at 0.105 kg ai/ha. In 16 pre-emergence trials and 16 post-emergence US trials matching GAP, residues in oat forage were < 0.01 mg/kg (32).

The Meeting estimated a median residue and a highest residue of 0.01 mg/kg for mesotrione in oat forage.

The registered use for mesotrione in sorghum in USA is one pre-emergence application at 0.224 kg ai/ha up to 21 days before planting. In 13 trials conducted according to GAP, residues in sorghum forage were < 0.01 mg/kg (13).

The Meeting estimated a median residue and a highest residue of 0.01 mg/kg for mesotrione in sorghum forage.

Hay

In 16 pre-emergence trials and 16 post-emergence trials conducted in oats in USA, matching GAP, residues in oat hay were < 0.01 mg/kg (32). Post-emergence application trials gave the same results.

In five trials conducted in millet at GAP, residues in hay were < 0.01 mg/kg.

The Meeting estimated a median residue of 0.01 mg/kg and a highest residue of 0.01 mg/kg for mesotrione in oat hay and millet hay.

Straw

Mesotrione is registered in paddy rice in Korea as post-planting into the water (5-7 days after transplanting) at 1x0.09 kg ai/ha and no PHI specified. In eight trials conducted in Japan at this GAP gave residues in straw of < 0.002 mg/kg.

The Meeting agreed to estimate a maximum residue level of 0.01* mg/kg for mesotrione in rice straw and fodder, dry

The Meeting estimates a median residue and a highest residue of 0.01 mg/kg for mesotrione in rice straw

Fate of residues during processing

A processing study conducted with soya bean containing 0.04 mg/kg mesotrione showed residues of 0.01 mg/kg in the meal and 0.07 mg/kg in flour, with calculated processing factors of 0.25 and 1.8 mg/kg, respectively. Residues in soya oil, milk, tofu, sauce and miso were < 0.01 mg/kg, with an estimated processing factor of < 0.25. Based on a STMR of 0.01 mg/kg for soya bean, dry, the Meeting estimated a STMR-P of 0.018 mg/kg in soya bean flour, and of 0.002 mg/kg for soya oil, milk, tofu, sauce and miso.

Residue in animal commodities

Farm dietary burden

The Meeting estimated the dietary burden of mesotrione in farm animals on the basis of the OECD Animal Feed data published in the 2009 FAO Manual, and the median and highest residue levels estimated at the present Meeting for oat and sorghum forage, oat hay and rice straw.

The maximum and the mean dietary burden was 0.03 ppm for cattle, 0.01 and 0.001 ppm, for swine, respectively, and 0 ppm for poultry.

Animal commodity maximum residue level

No feeding study on mesotrione was provided to the Meeting. The metabolism study conducted with cattle at 10 ppm, gave residues of mesotrione up to 0.02 mg/kg in tissues and milk. Swine fed with radiolabeled mesotrione at 6 ppm gave residues of 1.5 mg/kg in liver, 0.09 mg/kg in kidney and 0.01 mg/kg in muscle. Interpolation of the residues found in the metabolism studies to what would be expected at the calculated dietary burden indicates that no residue will exceed 0.0025 mg/kg (in swine liver).

The Meeting agreed to estimate a maximum residue level of 0.01* mg/kg for mesotrione in milks, edible offal (mammalian) and meat (from mammals other than marine mammals).

The Meeting also estimated a STMR of 0 for mesotrione in milk and meat (from mammals other than marine mammals), and edible offal (mammalian).

Metabolism study conducted with poultry at 11 ppm showed mesotrione residues of 1.1 mg/kg in liver, 0.03 mg/kg in fat, < 0.01 mg/kg in meat and 0.02 mg/kg in eggs. As the dietary burden for poultry is 0, the Meeting agreed to estimate a maximum residue level of 0.01* mg/kg, and a STMR and a HR of 0 mg/kg for mesotrione poultry meat, poultry offal and eggs.

RECOMMENDATIONS

Definition of the residue (for compliance with the MRL and for estimation of dietary intake for plant and animal commodities): mesotrione.

The residue is not fat soluble.

DIETARY RISK ASSESSMENT

Long-term intake

The IEDI of mesotrione based on the STMRs estimated by this Meeting for the 17 GEMS/Food regional diets were 0% of the maximum ADI of 0–0.3 mg/kg bw (see Annex 3 of the 2014 Report). The Meeting concluded that the long-term dietary intake of residues of mesotrione is unlikely to present a public health concern.

Short-term intake

The 2014 JMPR decided that an ARfD is unnecessary for mesotrione. The Meeting therefore concluded that the short-term intake of residues of mesotrione is unlikely to present a public health concern.