



COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

MELOXICAM (Extrapolation to rabbits and goats)

SUMMARY REPORT (7)

1. Meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class belonging to the group of enolic acids. Meloxicam is used in cattle for the treatment of acute respiratory infection in combination with appropriate antibiotic therapy to reduce clinical symptoms, for the treatment of diarrhoea in combination with oral rehydration therapy and adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. In swine meloxicam is used in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation and for adjunctive therapy in the treatment of puerperal septicaemia and toxæmia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy. In horses meloxicam is indicated for the reduction of inflammation and relief of pain associated with chronic musculoskeletal disorders. In bovines a single dose of 0.5 mg/kg bw by the intravenous or the subcutaneous route is indicated. In swine, 0.4 mg meloxicam/kg bw/day are administered intramuscularly for up to 2 consecutive days. For horses meloxicam is given intravenously as one daily administration of 0.6 mg meloxicam/kg bw/day and orally at a dosage of 0.6 mg/kg bw, once daily, up to 14 days.

The Committee for Veterinary Medicinal Products (CVMP) previously established an ADI of 1.25 µg/kg bw (i.e. 75 µg/person) for meloxicam, by applying a safety factor of 100 to the LOEL of 0.125 mg/kg bw for effects on the length of gestation in a reproductive toxicity study in Sprague Dawley rats.

Meloxicam is currently included in Annex I of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Meloxicam	Meloxicam	Bovine, porcine, <i>Equidae</i>	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	
		Bovine	15 µg/kg	Milk	

2. A request was submitted to the EMA for the extrapolation of the existing entry in Annex I of Council Regulation (EEC) No. 2377/90 for bovine and porcine species to goats and rabbits. The scientific justification for this extension was assessed taking into account the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMA/CVMP/187/00-FINAL).

The proposed intended indication for rabbits is reduction of post-operative pain, and for goats for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy and for use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical symptoms. In goats a single dose of 0.5 mg/kg bw by the intravenous or the subcutaneous route is proposed. In rabbits no specific dose has been proposed.

In setting the ADI in the original assessment of meloxicam, the data summarised in the paragraphs below were considered.

3. Meloxicam inhibits the synthesis of prostaglandin PGE₂ by inhibiting the constitutive cyclooxygenase effects: meloxicam has anti-inflammatory, anti-pyretic and analgesic properties and the inducible cyclooxygenase. Compared to several other NSAID's tested meloxicam was shown to be the most selective inhibitor of inducible cyclooxygenase activity.

Primary pharmacological in several species including humans, probably due to inhibition of inducible cyclooxygenase. Water-soluble forms of meloxicam showed identical pharmacological activity but were in most cases slightly more potent than meloxicam. Meloxicam had no effect on hexobarbitone sleeping time in mice. Furthermore, meloxicam had minor or no effects on the cardiovascular and respiratory systems in anesthetized cats and dogs as well as conscious dogs and in the guinea pig Langendorff preparation. Meloxicam had no anticonvulsant activity and did not affect the motility sensory function or reflexes in mice.

Secondary pharmacological effects: the main side-effects of meloxicam are ulcerogenic activity in the gastro-intestinal tract, nephrotoxicity and disturbances of reproduction, probably due to inhibition of constitutive cyclo-oxygenase. Treatment of rats with meloxicam was associated with minor reductions in urine volume, urine sodium and a marked increase in uric acid excretion as well as an increase in urinary potassium.

4. The three main metabolites (5-hydroxymethyl-, 5-carboxy- and oxalyl-metabolite) of meloxicam found in rats and humans, showed negligible activity when tested for anti-inflammatory activity and cyclooxygenase inhibition.
5. Pharmacokinetic studies were conducted in rats, mice, dogs, mini-pigs (intravenous and/or orally, single and repeated administration) and the target animal cattle (single dose of 0.5 mg/kg bw intravenously and subcutaneously to calves and repeated dosing of 0.7 mg/kg bw for 5 days to calves) with unlabelled or ¹⁴C-labelled meloxicam.

Meloxicam was well absorbed after oral administration in mice and dogs, with the oral bioavailability being at least 70% in mice and 100% in dogs. In calves the availability after subcutaneous administration was variable with a calculated mean of 92% compared to intravenous administration. Substance concentrations in blood were found to decline with elimination half-lives of approximately 4 to 6 hours in mice and mini-pigs, 20 to 58 hours in rats and dogs and 24 to 28 hours in calves. Extensive oral absorption and bioavailability and a relatively long half life, resembling that found in rats and dogs, have also been found for meloxicam in humans.

6. Sex and strain differences in the pharmacokinetics of meloxicam were found in rats. Thus blood substance concentrations in female rats were 2 to 4 times greater than those in males after a single dose and at steady-state. A longer drug half-life was also observed in female (38 to 58 hours) than in male rats (13 to 36 hours), and excretion in females was slower. Evidence for a similar sex difference was neither found in other laboratory species tested nor in the target species.

Blood substance levels in pigmented animals were 6 to 10 times lower than in albino rats, C_{max} was attained much more rapidly (0.5 to 1 hours) and drug excretion was also more rapid in pigmented than in non-pigmented rats.

7. Autoradiography and measurement of the total radioactivity showed that meloxicam was distributed to all tissues in the rat and penetrated the central nervous system (small amounts), muscle layers and inflamed joints. There was no evidence for retention or accumulation in any tissues including pigmented tissues after single or repeated dosing.

Meloxicam crossed the placenta of pregnant rats and was detected in foetal tissue at levels similar to those found in the placenta, which remained below plasma drug levels. Meloxicam and/or metabolites were excreted in rat milk, with levels in milk increasing relative to those in plasma over 1 to 24 hours after administration. In the single dose study as well as in the repeated-dose study in calves, the highest concentrations of radioactivity were in liver, followed by kidney and bile (single dose study) at all sacrifice time points (up to 8 days). Comparatively low concentrations were found in skeletal muscle and fat.

8. Meloxicam was found to be highly bound to plasma proteins in rats (greater than 99%), mice, dogs and mini-pigs (greater than 96%). In calves plasma protein binding was found to be greater than 96.5% *ex vivo* and greater than 98% *in vitro*.
9. Radiolabelled meloxicam was found to be excreted in both urine and faeces. Excretion was predominantly via urine in rats and mice (approximately 65 to 70% of the dose) and equally divided between urine and faeces in humans, mini-pigs and cattle. There were no differences in drug excretion after oral or intravenous administration, and minor differences in drug excretion with repeated administration in mini-pigs and rats. The majority of the excreted dose was recovered within 2 to 3 days after treatment in mice, mini-pigs and cattle (after the last dose in the repeated dose study) and within 1 to 4 days in rats.
10. Meloxicam is extensively metabolised in rats, mice, mini-pigs, humans and cattle and the metabolite profile in plasma and excreta is qualitatively similar in rats, mini-pigs and cattle (including edible tissues). In urine less than 10% of a dose was excreted as unchanged meloxicam. The major metabolites found in all species were the 5'-hydroxy methyl- (10 to 50% of radioactivity) and 5'-carboxy- (4 to 35% of radioactivity) metabolites. The oxalyl metabolite was found in humans (30 to 35%), rats (25 to 30%) and cattle (4 to 10%), but not in mini-pigs and mice. A highly polar metabolite was found in cattle urine, but not in urine from the other species. Repeated administration of meloxicam produced no qualitative changes of metabolism compared to single administration. Rat milk contained 20% higher levels of metabolites than plasma. Studies with the 5'-hydroxymethyl and the 5'-carboxy metabolites in rats indicate a rapid excretion with the major portion of both compounds eliminated within 1 to 2 hours.
11. The acute oral toxicity for meloxicam has been investigated in rats (strains: Sprague Dawley and Chbb:THOM), minipigs, mice and rabbits. For Sprague Dawley rats the oral LD₅₀ was greater than 200 mg/kg and 98.4 mg/kg for males and females, respectively. For Chbb:THOM rats the oral LD₅₀ was 83.5 mg/kg (females and males together). In mini-pigs the oral LD₅₀ was approximately 1600 mg/kg, in mice 470 mg/kg and in rabbits 320 mg/kg.
12. Repeated-dose toxicity was evaluated in three strains of rats (Chbb:THOM, Sprague Dawley and Wistar (intravenously: 4 weeks, orally: 4, 13, 26, 52 and 78 weeks)), mice (orally: 13 weeks), micro- and mini-pigs (intravenously: 4 and 5 weeks and orally: 13 and 52 weeks). Shorter term tolerance studies were also performed in dogs (orally: 3 and 4 weeks). Doses in rats, mice, pigs and dogs were in the dose range of 0.2 to 10 mg/kg bw, 8 to 35 mg/kg bw, 1 to 10 mg/kg bw and 0.1 to 1.2 mg/kg bw, respectively. The primary target organs for toxicity were the gastrointestinal tract and kidneys. Deaths during treatment with meloxicam were associated with gastric and renal toxicity. Gastrointestinal lesions consisted of ulcers, particularly in the pyloric region of the stomach, but also in the duodenum and in some animals further along the small intestine, coagulated blood in gastrointestinal tract, peritonitis, gastric erosion, gastric dilation and/or callous thickening. Renal changes consisted of scarring, granular surface, presence of gritty concretum, necrosis and pyelonephritis. Organ weight analysis revealed weight increases of the spleen and kidneys. Once the treatment ceased the severity of toxicity and extent of reversibility were dependent on dose and duration of treatment. Female rats were more severely affected than male rats, consistent with higher blood levels of meloxicam in females compared to males. The sex difference in sensitivity was not observed in mini-pigs and mice.

In rats, an oral NOEL of 0.2 mg/kg bw was established in the 52-week feeding study in Wistar rats as well as after intravenous treatment for 4 weeks in Chbb:THOM rats. Minipigs were relatively insensitive to meloxicam with a NOEL of 1 mg/kg bw derived from a 13 weeks and a

52 weeks study following oral administration. In dogs a NOEL of 0.4 mg/kg was determined in the 4-week study. However, in the 3-week study occult blood was observed even in the lowest dose (0.4 mg/kg bw) and a NOEL could not be determined.

13. Tolerance studies have been performed in cattle. Meloxicam was administered in doses of 0.5 to 1.5 mg/kg bw intravenously in calves for 5 days. Meloxicam was well tolerated in calves at the doses tested.
14. Reproductive toxicity studies in Sprague Dawley rats cover all stages of the reproduction cycle, segments I-III but the segments were performed separately and with different dosage regimes. Treatment with meloxicam was associated with reduced implantations, increases in resorption rate, prolonged pregnancy and decreased pup viability. A segment I study (doses in males: 0, 1, 2.5 and 9 mg/kg/day 9 weeks prior to mating and 3 weeks during mating, in females: 0, 1, 2.5 and 5 mg/kg bw/day 2 weeks prior to mating until day 7 of pregnancy) resulted in a dose-dependent reduction in implantation rate and increased resorption rate. Fertility indices were unaffected. In the segment II study dosing was 1 to 4 mg/kg bw during the organogenesis (day 7 to 17 of pregnancy). In this study prolongation of pregnancy and increases in foetal deaths (stillbirths) in the treated groups were observed. In a segment III study (0, 0.125, 0.25, 0.5 mg/kg bw from gestation day 17 until day 21 of lactation) dose dependent maternotoxic and foetotoxic effects (prolongation of gestation period and duration of delivery, stillbirths, mortality in new-borns and reduced viability of new-borns of treated dams, gastrointestinal lesions) were observed and may be attributable to the inhibition of prostaglandin synthesis induced by meloxicam. Statistical analysis was performed with two different methods. These analyses showed a significant effect only for prolonged gestational length at the lowest dose (21.94 ± 0.61 days compared to 21.35 ± 0.29 days in the control group) tested. This dose (0.125 mg/kg bw) can be regarded as a LOEL. The NOEL for embryotoxic effects in Sprague Dawley rats was 1 mg/kg bw.
15. Teratogenicity studies have been performed in rats (strains: Sprague Dawley and Chbb:THOM) and rabbits (Chbb:HM) at doses of 1 to 4 mg/kg bw in rats and 1 to 80 mg/kg in rabbits. There was no evidence for teratogenic activity in these studies. However, meloxicam showed embryotoxic effects at the lowest doses tested (1 mg/kg) in Chbb:THOM rats and in rabbits. For maternotoxicity, NOELs of 1 and 20 mg/kg bw were identified in Chbb:THOM rats and rabbits, respectively.
16. Meloxicam did not demonstrate genotoxic activity in properly performed gene mutation assays (*Salmonella typhimurium* and *E.Coli* reversion assays, and HGPRT locus in Chinese hamster lung fibroblasts) or Chromosome damage assays (human lymphocytes *in vitro* and micronucleus test in mice *in vivo*). Meloxicam was also negative in a host-mediated gene mutation assay, but this test was not considered reliable for the reason that the positive controls were also without activity. No DNA damage assay has been performed. It is concluded that meloxicam showed no mutagenic potential in the tests performed.
17. No evidence for carcinogenic activity was found in two-year dietary studies in mice and rats with doses of 2, 4 and 8 mg/kg bw daily and 0.4, 0.6 and 0.8 mg/kg bw daily, respectively. This is consistent with the negative findings in the mutagenicity tests.
18. The phototoxic potential of meloxicam was assessed in the human erythrocyte lysis test, rat mast cell degranulation test and in a test of cytotoxicity in murine fibroblasts. Meloxicam showed no phototoxic potential in the first two tests, but was dose-dependently moderately phototoxic in the third assay. In conclusion, meloxicam did not meet the criteria for a phototoxic agent, i.e. positive in two out of three tests.
19. Meloxicam did not show any sensitising potential in Magnusson and Kligman tests using either a parenteral formulation or a gel formulation of meloxicam. Meloxicam also showed no immunogenic activity in mice after an injection in the hind-paw.
20. Studies on the microbiological properties of meloxicam were not submitted and are considered not to be necessary in view of the nature of the compound.

21. Meloxicam is used in human medicine for treatment of rheumatoid arthritis and osteoarthritis. Daily oral doses of 7.5 mg or 15 mg per person are recommended, corresponding to approximately 0.125 or 0.25 mg/kg bw/day. Clinical trial studies including approximately 6000 patients or healthy volunteers have been submitted. However, these studies did not provide sufficient data to enable the establishment of a pharmacological ADI in humans.
22. A pharmacological NOEL could not be derived from the submitted animal or human data. However, based on the data submitted, the rat appears to be the most sensitive species to meloxicam, with Sprague Dawley rats being more sensitive than Wistar rats and Chbb:THOM rats. In the segment III-study in Sprague Dawley rats statistically significant longer length of gestation was recorded in the lowest dose group (21.94 ± 0.61 days compared to 21.35 ± 0.29 days in the control group) treated with meloxicam. Although, the difference in the length of gestation is significantly increased in the lowest dose group, it is only a marginal effect. Thus, 0.125 mg/kg bw can be regarded as a LOEL for establishment of an ADI. A safety factor of 100 may be employed as the LOEL is based on dose dependent effects and the effect is considered to be of no biological importance. A toxicological ADI of 1.25 µg/kg bw (equivalent to 75 µg for a 60 kg person) can be established for meloxicam.
23. The metabolism and excretion of meloxicam was investigated in mini-pigs after oral (3.5 and 10 mg/kg) and intravenous administration (10 mg/kg) of ^{14}C -meloxicam in two non-GLP studies. Meloxicam was found to be highly bound to plasma proteins (about 96%) and the concentrations in blood were found to decline with an elimination half-life of approximately 6 hours. Excretion was equally divided between urine and faeces and the majority of the excreted dose was recovered within 2 to 3 days. Meloxicam was extensively metabolised in mini-pigs and the metabolite profile was qualitatively similar in plasma and excreta. In urine less than 3% of a dose was excreted as unchanged meloxicam. In faeces meloxicam accounted for 17% of the radioactivity from orally dosed mini-pigs, but was not detected in intravenously dosed animals. A large proportion (60 to 80%) of the plasma radioactivity was unchanged meloxicam. The major metabolites found in plasma, urine and faeces were the 5-hydroxymethyl and the 5-carboxy-metabolites. Four hours after the oral dose of 3.5 mg ^{14}C -meloxicam the highest concentrations in edible tissues were found in liver and kidney. The concentration in liver was about 20 times higher than that of muscle.
24. A GLP compliant metabolism and residue study was performed in pigs. Sixteen pigs (Large White Hybrids, bodyweight 46.5 to 68.5 kg, 5 months of age) received an intramuscular injection of 0.4 mg ^{14}C -meloxicam/kg bw once daily for 2 consecutive days. The animals were slaughtered in groups of 2 females and 2 males at 4 hours and at 2, 4, and 8 days after the second dose. At slaughter, samples of liver, kidneys, skeletal muscle, fat (renal and omental) and muscle and skin+fat from the two injection sites were taken for analysis of total radioactivity by liquid scintillation counting. The concentrations of the parent compound meloxicam were determined using an HPLC method with LC-MS/MS detection.

Urine and faeces were collected from 4 pigs during the dosing period and up to 4 days post last dose. Metabolite profiles were obtained in selected samples of urine, faeces and tissues by HPLC and TLC. In plasma, concentrations of radioactivity were determined up to 96 hours following the second dose by LSC and concentrations of meloxicam were determined by HPLC.

Approximately 39% and 45% of the administered radioactivity was excreted in urine and faeces, respectively. Parent compound was only a minor component and accounted for 2.5% and 2.8% of the urinary and faecal radioactivity, respectively. The major urinary metabolites were the 5-carboxy and 5-hydroxymethyl metabolites accounting for 20 to 33% and 31 to 43% respectively in urine 24 hours after the second dose. A polar metabolite accounted for 12 to 16% but was not identified. Four other unknown metabolites were separated and represented less than 10% of the urinary radioactivity.

The major faecal metabolite excreted during 5 days was the 5-carboxy metabolite, which accounted for approximately 65% of the faecal radioactivity.

The major component detected in all tissue extracts from the 4-hour sacrifice corresponded to unchanged meloxicam (36 to 52%) except for liver where it was the polar metabolite. In liver meloxicam accounted for 17% of the radioactivity and the polar metabolite accounted for 37%. Low levels (1 to 8%) of radioactive components corresponding to the 5-carboxy- and 5-hydroxymethyl metabolites were also detected in most tissues. In the liver and kidney extracts from samples obtained at the 2- and 4-day sacrifices, no meloxicam was detected.

The metabolism in the pig is qualitatively similar to rats, mini-pigs, humans and cattle although quantitatively there are differences. The major metabolites found in all species were the 5-hydroxy- and 5-carboxy-metabolites.

Plasma radioactivity concentrations increased to a maximum mean concentration of 1662 ng equivalents/ml at 1 hour after the second dose and then declined to a mean concentration of 19 ng equivalents/ml at 96 hours after administration. Pharmacokinetic analysis revealed a C_{max} of 1730 ng equivalents/ml and a t_{max} of 1 hour.

The concentrations of meloxicam in plasma after the second dose increased to a maximum mean concentration of 1856 ng/ml at 1 hour and thereafter declined to reach a mean concentration of 156 ng/ml at 12 hours after administration. Meloxicam was not detected in the plasma of three of the four animals beyond 12 hours after administration and was not detected in any animal beyond 24 hours after administration. Pharmacokinetic analysis revealed a C_{max} of 1885 ng/ml at 1 hour after the second dose. The elimination was rapid and the terminal half-life was estimated to 2.5 hours.

25. The pharmacokinetic study in pigs (16 animals receiving an intramuscular injection of 0.4 mg ^{14}C -meloxicam/kg bw once daily for 2 consecutive days) provided data on tissue residues up to 8 days after administration. Concentrations of radioactivity in edible tissues were highest in liver and kidney at each slaughter time. The mean total radioactive residue concentrations fell from 999 and 1450 μg equivalents/kg in liver and kidney, respectively, at 4 hour after last administration, to 175 and 105 μg equivalents/kg, respectively, at 2 days after last dose, to 91.1 and 63.6 μg equivalents/kg 4 days after last administration and to 44.8 and 20.5 μg equivalents/kg at 8 days after last administration. Levels of radioactivity in muscle were low, 55.6 and 7.6 μg equivalents/kg at 4 hour and 2 days, respectively. No radioactive residues could be detected at later time-points. Levels of radioactivity in fat and skin+fat were only detected at the 4-hour sacrifice time, 189 and 118 μg equivalents/kg, respectively.

Concentrations of meloxicam in edible tissues above the limit of quantification (10 $\mu g/kg$) were only detected at 4 hour after slaughter except in a few samples of injection sites. The mean concentrations were 446, 845, 37.6, 77.7 and 83 $\mu g/kg$ in liver, kidney, muscle, fat and skin+fat, respectively.

Ratios of meloxicam to total radioactive residues could only be calculated at 4 hours after administration as no significant meloxicam residues were detected at later time-points. Ratios of meloxicam to total residues were 0.44, 0.56, 0.67, 0.42 and 0.70 in liver, kidney, muscle, fat and skin+fat, respectively.

26. In cattle, residue depletion of ^{14}C -meloxicam was investigated following repeated administration of 0.7 mg/kg bw subcutaneously for 5 days to sixteen Hereford/Friesian calves. The dose regimen used does not correspond to the recommended one i.e. 0.5 mg/kg bw/day.

Four animals were sacrificed at 8 hours, 2, 4 and 8 days after the last administration. The total radioactive residue concentrations 8 hours post last administration were: 8540 μg equivalents/kg in liver, 5070 μg equivalents/kg in kidney, 520 μg equivalents/kg in muscle, 720 μg equivalents/kg in renal fat, 550 μg equivalents/kg in omental fat and 5210 μg equivalents/kg in the injection site. The concentrations declined to reach 1960 μg equivalents/kg in liver, 1480 μg equivalents/kg in kidney, 60 μg equivalents/kg in muscle, 90 μg equivalents/kg in renal fat, 70 μg equivalents/kg in omental fat and 230 μg equivalents/kg in the injection site 4 days after last administration. After 8 days, total residues could only be measured in liver (660 μg equivalents/kg) and kidney (220 μg equivalents/kg).

27. In all edible tissues from cattle, the major single component, in contrast to the profile in urine, was parent meloxicam. The concentrations of unchanged meloxicam were determined by a validated HPLC procedure in muscle and liver and the ratio of parent compound to total residues was determined. At 8 hours and 2 days more than 85% of radioactivity was associated with meloxicam in liver. At 4 days the ratio was approximately 55% and at 8 days approximately 12%. In muscle more than 90% of the radioactivity was parent compound at the three first sacrifice times. At 8 days a ratio of parent compound to total residues could not be established because both the total and the marker residues were below quantifiable levels. The ratio of unchanged meloxicam to total residues in kidney and fat was determined using radio-HPLC and two radio-TLC methods. For kidney the mean overall ratio determined using all radioanalytical results was approximately 40% at 8 hours, 50% at 2 days, 44% at 4 days and 20% at 8 days. For fat this ratio was approximately 60% at 8 hours, thereafter radioactivity was too low for analysis. The concentrations of meloxicam in kidney and fat were not determined by the validated HPLC method, thus the relative distribution of the marker between the target tissues could not be established in precise quantitative terms.
28. A depletion study at the recommended dose of administration in cattle was provided, in which radiolabelled meloxicam was administered subcutaneously as a single dose of 0.5 mg/kg bw.

¹⁴C-Meloxicam was administered subcutaneously as a 0.5% formulation to groups of 4 young cattle. The mean total radioactive residue concentrations fell from 781, 689, 42 and 138 µg equivalents/kg in liver, kidney, muscle and injection site, respectively, at 2 days after administration, to 123, 72, lower than 10 and 35 µg equivalents/kg, respectively, at 4 days after administration, to 242, 120, lower than 13 and 21 µg equivalents/kg, respectively, at 6 days after dosing and to 120, 48, lower than 9 and 34 µg equivalents/kg respectively at 8 days after administration.

Meloxicam concentrations were measured by HPLC and the mean concentrations were 570, 534, 43 and 73 µg/kg in liver, kidney, muscle and injection site, respectively, at 2 days after administration. Then, in liver and in kidney, they fell to 28 and 29 µg/kg, respectively, at 4 days after administration, to 54 and 56 µg/kg, respectively, at 6 days after administration and to 22 and 25 µg/kg, respectively, at 8 days after administration. In muscle and in the injection site the concentrations of meloxicam were, in most of the samples, either below the limit of quantification (10 µg/kg) or below the limit of detection (2 µg/kg).

Fat was not analysed in this study as no MRL has been established for fat.

According to this study ratios of marker residue to total residues of 0.23 and 0.4 were retained for liver and kidney, respectively, at 4 days post administration, the nearest time-point when total residues in the standard food package are expected to fall below the ADI. A ratio of 1 for muscle was determined at 2 days post administration, the values in muscle being too low at 4 days to establish such a ratio.

29. A milk residue depletion study was performed where ¹⁴C-meloxicam was administered subcutaneously at the recommended dose regimen as a 2% formulation to 8 lactating cows (4 low milk yield and 4 high milk yield). Milk was collected twice daily, once in the morning and once in the afternoon after an interval of approximately 6 hours, for 10 days.

Blood samples were also taken and the plasma concentration profile showed that maximum concentration of meloxicam was reached approximately 4 hours after treatment. The mean peak plasma concentrations were 2875 µg/l for low milk yield cows and 2495 µg/l for high milk yield cows. The plasma half-life of meloxicam was approximately 17.5 hours. The pharmacokinetic profile of meloxicam in lactating cows was similar to that of non-dairy cattle.

The metabolism of meloxicam was similar in low and high yield cows. Meloxicam accounted for approximately 80% of the radioactivity in milk. Two other components were also detected, the sodium salt of the oxoacetic acid moiety of meloxicam and 4-hydroxy-N-(5-hydroxymethyl)-2-thiazolyl)-2-methyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide. 4-Hydroxy-N-(5-hydroxymethyl)-2-thiazolyl)-2-methyl-2H-1,2-benzothiazin-3-carboxamide-1,1-dioxide was the major metabolite accounting for 10 to 20% of the radioactivity. The sodium salt of the oxoacetic acid

moiety of meloxicam was a minor component accounting for approximately 1% of the radioactivity. Both metabolites found in milk were seen in non-lactating cattle, rats and humans.

The highest mean concentrations of radioactivity were detected in milk collected at 6 hours post-administration (low milk yield, 374 µg equivalents/kg; high milk yield, 394 µg equivalents/kg). The corresponding mean concentrations of meloxicam measured by HPLC were 347 µg/kg and 325 µg/kg, respectively. Mean concentrations of radioactivity then declined to 17 µg equivalents/kg (low yield) and 15 µg equivalents/kg (high yield) at the day 5 morning milking with corresponding mean meloxicam concentrations of 13 µg/kg and 10 µg/kg, respectively. Concentrations of radioactivity were at or below the limit of detection of 1 µg/kg in all animals at the day 9 morning milking and the mean concentrations of meloxicam at the same time-point were below the limit of quantification of 2.5 µg/kg. Mean concentrations of meloxicam in the afternoon milk samples declined with half-lives of 26.5 and 21.7 hours in the high and low yield animals, respectively.

In most milk samples the proportions of meloxicam collected up to 7 days were higher than or equal to 75% of the total radioactive residues and a ratio of 0.75 can be used for the calculation of the MRL in milk.

30. Considering the knowledge on the variation of residue depletion within classes of animals and therefore on the exposure assessment the risk characterisation should also not differ substantially within an animal class. Therefore, an extrapolation of MRLs from pigs and bovines to rabbits and goats should not be problematic and is considered as the default approach according to the guideline “Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMA/CVMP/187/00-FINAL)” .
31. In line with the MRLs for pig and bovine tissues and bovine milk, and in application of the above-mentioned guideline the marker residue meloxicam was retained for the species rabbits and goats.
32. A routine analytical method based on HPLC with LC-MS/MS detection for determination of meloxicam in porcine tissues is available in the ISO 78/2 format and validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union. The limit of quantification was 10 µg/kg for all porcine edible tissues and the limit of detection was 5.7 µg/kg for muscle, 1.8 µg/kg for liver, 2.0 µg/kg for kidney, 2.2 µg/kg for skin/fat and 3.0 µg/kg for fat.

A routine analytical method based on HPLC for determination of meloxicam in bovine tissues was presented in the ISO 78/2 format and validated for muscle, liver and kidney. The limit of quantification is 10 µg/kg for all target tissues. The limits of detection are 2 µg/kg for muscle, 3 µg/kg for liver and 1.5 µg/kg for kidney. A routine analytical method based on HPLC for determination of meloxicam in milk is available in the ISO 78/2 format and validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union. The limit of quantification was 2.5 µg/kg and the limit of detection was 1.5 µg/kg.

Applicability of these methods to rabbit and caprine tissues and caprine milk should not be problematic and therefore from this aspect extrapolation to the tissues of rabbits and tissues and milk of goats would be possible.

33. In application of the guideline “Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMA/CVMP/187/00-FINAL)” it was considered possible to further extrapolate the existing MRLs for bovine and porcine species to goats and rabbits. Information on residue data from meat from ovine species was not available, to allow for extrapolation to all mammalian species.

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 1.25 µg/kg bw (75 µg/person) was previously established for meloxicam,
- meloxicam was retained as the marker residue,
- MRLs have been established for the major species bovine and porcine, these MRLs are identical to those recommended for rabbits and caprine species,
- a validated analytical method for monitoring residues from porcine and bovine species including milk, is available and the method is also considered to be applicable to rabbit tissues, caprine tissues and caprine milk;

the Committee recommends the establishment of MRLs for meloxicam in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Meloxicam	Meloxicam	Rabbits, caprine	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	
		Caprine	15 µg/kg	Milk	

The daily intake of meloxicam from residues will represent about 97% of the ADI.