NSAIDs are among the most frequently used drug treatments in Europe and the United States, accounting for approximately 5% of all prescriptions (Baum et al., 1985; Wynne and Campbell, 1993). Moreover, the use of NSAIDs is increasing because they remain first-line drug therapy for a wide range of rheumatic conditions. This increase is in part the result of the increasing population of elderly patients, who constitute the group of patients with greatest demand for these agents; it is estimated that more than half of all patients using NSAIDs are >60 years old (Baum et al., 1985).

Meloxicam [4-hydroxy-2-methyl-5-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, UH-AC 62 XX; Boehringer Ingelheim] (fig. 1) is a novel NSAID of the acidic enolcarboxamide class. Studies of meloxicam treatment of animals with adjuvant arthritis revealed marked amelioration of the symptoms of bone and cartilage destruction and the systemic signs of immunologically induced inflammation (Engelhardt et al., 1995). Meloxicam has a high intrinsic activity combined with a low ulcerogenic potential (i.e. a high therapeutic index) (Engelhardt et al., 1996b). The therapeutic index of meloxicam is higher than that of other NSAIDs, including piroxicam, diclofenac, and indomethacin (Engelhardt et al., 1996b).

Fig. 1. Chemical structures of meloxicam and its principal metabolites, the 5'-carboxy metabolite (UH-AC 110 SE) and the 5'-hydroxymethyl metabolite (AF-UH 1 SE).

Meloxicam preferentially inhibits cyclooxygenase-2, which is induced by inflammatory stimuli in pathophysiological conditions, rather than cyclooxygenase-1, which is responsible for physiological processes, e.g. in the stomach (Churchill et al., 1996; Engelhardt et al., 1996a; Pairet and Engelhardt, 1996). Despite the structural relationship to other NSAIDs (Woolf and Radulovic, 1989; Olkkola et al., 1994), the introduction of the methyl group in the thiazolyl moiety of meloxicam has facilitated the formation of metabolites (Schmid et al., 1995b) that undergo fast elimination, leading to a shorter t1/2, in comparison with piroxicam and tenoxicam. The pharmacokinetics of meloxicam have been investigated in a number of animal species, including mice, rats, dogs, mini-pigs, and baboons, to provide comprehensive profiles and to determine which animal species exhibits a profile most closely resembling the pharmacokinetic profile in humans.

1 Abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; CL, clearance of drug from plasma; Cmax, maximum concentration of drug in plasma; F, bioavailability factor; id, intraduodenal; MRT, mean residence time; Vss, apparent volume of distribution under steady-state conditions; t1/2, terminal elimination rate constant; Vmax, apparent volume of distribution during the terminal phase; AUC, area under the plasma concentration-time curve; P450, cytochrome P450.

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Materials and Methods

Radiolabeled Compound. Meloxicam was radiolabeled by introducing a $^{14}$C atom into the carboxamide group of the molecule (fig. 1), at a position that was considered least likely to be affected by metabolic transformation. In all studies, the specific radioactivity required was obtained by dilution with nonradiolabeled meloxicam.

Analytical Procedures, Radiometry. The concentrations of $[^{14}C]$meloxicam and its metabolites in blood, plasma, tissue, urine, bile, and feces were measured using a liquid scintillation counter (Packard TriCarb 3385). Quench correction was made using the external standard ratio, and the radioactivity measured in dpm per milliliter of blood was converted into the concentration of drug and metabolites by division by the specific radioactivity of $[^{14}C]$meloxicam. Because the method measures both meloxicam and radioactive metabolites of meloxicam, concentrations were expressed as equivalents of $[^{14}C]$meloxicam. The radioactivity in urine, feces, and bile was expressed as a percentage of the radioactivity administered. Based on the specific radioactivity used, the lower detection limit was 2 ng/eq/mL liquid or 2 ng/eq/g tissue.

HPLC Assay for Meloxicam Analysis. The concentration of the parent compound in plasma was also determined by a specific HPLC method. Plasma samples (50 μL) were applied to precolumns filled with Bondapak C18 Corasil material, with a stream of 0.01 M sulfuric acid for 4 min. The extract was then backflushed with eluent (methanol/water/acetonitrile/glacial acetic acid, 600: 500:50:20, v/v containing 1.01 g of heptanesulfonic acid in 1.17 liters), and chromatographic separation was achieved with a Hypersil ODS column (125 × 4.6 mm). Eluting peaks were quantified by means of UV detection at 355 nm and were evaluated by the external standard method. The HPLC assay allowed concentrations as low as 0.05 mg/Liter to be quantified in plasma from various species. The assay was validated from 0.05 to 2.5 mg/Liter over 3 days.

Whole-Body Autoradiography and Tissue Distribution. Tissue distribution in rats was studied by whole-body autoradiography. The animals were anesthetized at various times after oral or iv administration of meloxicam and were killed after the removal of a blood sample. The bodies were frozen, and then 30-μm serial sections were prepared according to the method of Ullberg (1954). X-ray-sensitive film (Osram M3; Agfa Gevaert) was exposed to the lyophilized sections for either 40–45 days (experiments using orally administered meloxicam) or 30 days (experiments using iv administered meloxicam).

After preparation of the histological sections described above, one to three samples were taken from each of the following tissues in the remainder of the frozen bodies: liver, lungs, brain, skeletal muscle, fat, and thymus gland. All samples were weighed, dried at 70°C overnight, and combusted in a sample oxidizer (Packard sample oxidizer 306). The radioactivity of the samples was measured using a liquid scintillation counter, and the concentration of meloxicam was calculated in microgram-equivalents per gram of organ. The concentration of radioactivity in the remaining organs was determined quantitatively by photometric comparison of the autoradiographs.

Tissue distribution in mini-pigs was investigated after exsanguination (after anesthesia) and preparation of organs. Gall bladder, urinary bladder, stomach, and small and large intestine were emptied, and the radioactivity of the contents was determined. Plasma, synovia (prepared from the knee joint), and the following organs were taken from the sacrificed animals: brain, hypophysis, eyes, submandibular gland, sublingual gland, parotid gland, thyroid gland, thymus, trachea, lungs, heart, stomach, small intestine, large intestine, liver, diaphragm, pancreas, spleen, kidneys, adrenal glands, testes, epididymis, skeletal muscle, skin, bone, and cartilage. No fat tissue was found in either animal. No thymus was found in the male animal. The isolated organs were weighed immediately after preparation.

Sampling of Biological Materials. Blood samples from mice and rats were obtained under halothane anesthesia by puncture of the orbital venous sinus. Urine and feces were collected over 48 hr (mice) or 96 hr (rats), and the radioactivity of the samples was determined.

For determination of the biliary excretion in rats, bile duct cannulation was performed under urethane anesthesia and bile samples were collected in fractions. Meloxicam was administered either into the duodenum (id) or into the tail vein (iv). For determination of the enterohepatic circulation (rats only), bile was collected from one group of animals (N = 3) for 6 hr after iv administration of meloxicam (1 mg/kg) and was stored on ice. The radioactive content of each bile sample was measured, and then samples were pooled, the combined amount of radioactivity was determined, and 1-mL portions of bile were administered id to animals of another group. The bile secreted by this second group of animals was collected in fractions over 6 hr, and the radioactivity of the samples was determined. In mini-pigs, bile was collected at the time of killing.

Preparation of Samples for Liquid Scintillation Counting. In general, each of two 100-μl portions of whole blood was hemolyzed in plastic vials with 1 ml of the tissue solubilizer Soluene 350 (Packard/isopropanol (1:2, v/v)) and decolorized with 0.2 ml of 30% H2O2; 3 hr later, 12 ml of Instagel (Packard) was added. After an overnight decay period, samples were measured using a liquid scintillation counter (Packard TriCarb 3385). Plasma was prepared by centrifugation of blood. Radioactivity was determined in duplicate 50–200-μl fractions.

For bile and synovial fluid, aliquots of 100 μl were used for counting. For measurement of biliary excretion in rats, the total fraction was used. The total volume of urine was determined, and then two 0.1–0.5-ml portions of urine were measured in the liquid scintillation counter after addition of 12 ml of Instagel, which was used as a cocktail for liquid scintillation counting. The fecal samples were made up to 80–120 ml with water and homogenized with an Ultra-Turrax homogenizer (Jahnke and Kunkel, Stauffen, Germany) after addition of 0.5 ml of n-octanol (antifoaming agent). Two or three 1.0-ml portions of the homogenate were added to combustion cones with combustion pads (for absorption). After drying at 70°C, samples were combusted in a sample oxidizer (model 306; Packard) and the radioactivity was measured.

The distribution of radioactivity between erythrocytes and plasma in vivo was investigated for rats. After oral administration of $[^{14}C]$meloxicam, 1.5 ml of blood was taken from three rats, at 2, 8, and 24 hr, by puncture of the orbital venous sinus. After determination of the radioactivity and hematocrit levels, the whole blood was centrifuged to separate the plasma. Two 0.2-ml samples of plasma in 12 ml of Instagel were used for measurement of radioactivity.

For the mini-pigs, the contents of the stomach and small intestine were homogenized, and 0.5-ml aliquots were dried and combusted in a sample oxidizer. Water was added to the content of the large intestine to yield a final volume of 5 liters. Homogenization was performed after the addition of 1–2.5 ml of n-octanol to prevent the formation of foam. Aliquots of 0.5 ml (in triplicates) were dried at 80°C overnight and combusted in a sample oxidizer. Bone and cartilage were dissolved in concentrated hydrochloric acid, and aliquots were dried and combusted in a sample oxidizer.

The following organs of the male mini-pig were subjected to special procedures. Water was added to brain and spleen, and homogenization was performed with a rotating-scissors homogenizer. Aliquots of 0.5 ml (in triplicates) were pipetted onto combustion pads, dried overnight at 80°C, and combusted in a sample oxidizer. Hypophysis, thyroid gland, and adrenal glands were dried at 80°C and then combusted in a sample oxidizer.

Metabolite Profile in Mice. The metabolite profile was established using an HPLC pump with a ternary gradient system and diode-array detector (HP 1090 M; Hewlett Packard, Waldbronn, Germany). The analyte (50–200-μl volume) was injected directly onto the analytical column (125 mm × 4.6-mm internal diameter, with a 20-mm guard column, filled with Hypersil ODS, 5-μm, material; Knauer, Berlin, Germany). The eluent was a gradient from 1% ammonium formate buffer, pH 6.8, to methanol, at a flow of 1 ml/min. The oven temperature was 28 ± 1°C.

For quantification of the radioactivity, the HPLC eluate was collected in scintillation vials, and the radioactivity was measured by liquid scintillation counting. UV detection was performed with a diode-array detector (HP 1040 M) at 363 nm.

Confirmation of the molecular structure was performed with HPLC/MS/MS (HP 1090 M pump and HP 1040 diode-array detector, both from Hewlett Packard, Böblingen, Germany, and TSQ 700 triple-stage quadrupole mass spectrometer with electrospray source from Finnigan MAT, Bremen, Germany). For the HPLC/MS/MS analysis, the enrichment buffer was 0.01 M ammonium acetate, pH 6.6, with a gradient from 0.01 M ammonium acetate to 100% methanol established within 18 min.

The enrichment column consisted of a 40-mm × 4.6-mm internal diameter Bishoff tube (Leönberg, Germany) filled with C18 Sepaplyte preparative grade, 40-μm, material (Analytichem, Harbor City, CA). The eluent was 1% ammonium formate buffer, with a flow rate of 1 ml/min, at room temperature.
Metabolite Profile in Rats. Plasma was extracted with an excess (5–10 times) of methanol; urine was lyophilized and the residue was dissolved in methanol. Lactated milk was extracted using an activated C18 cartridge. Organic extracts of plasma, urine, bile, feces, and lactated milk, as well as samples of urine deconjugated by enzyme and acid hydrolysis, were applied as methanolic solutions, in bands, to the TLC plates. The solvent system for chromatography consisted of chloroform/methanol/concentrated ammonium (80: 20:1, v/v). After chromatography, the TLC plates were evaluated with a TLC linear analyzer (Berthold LB 2820). In addition, X-ray film was exposed to the plates to assess the patterns of metabolites. To quantify the separated spots of radioactivity, the paths were divided into zones. The zones of adsorbent corresponding to radioactive areas on the TLC plates were scraped off and transferred to vials, and 0.5 ml of methanol/chloroform (1:1, v/v) was added to each vial to extract the radioactivity from the silica gel. The radioactivity was measured by liquid scintillation counting in 12 ml of Instagel. Nonradioactive components on TLC plates were visualized by quenching of fluorescence at 254 nm.

Metabolite Profile in Mini-pigs. Aliquots of plasma, bile, and urine were analyzed for the parent compound and metabolites using a Varian 5000 HPLC system (Varian, Darmstadt, Germany), with ternary gradient capability, coupled to a Ramona D flow-through scintillation counter (Isomess), Negretti and Zamba sampling valve (Gynkotek), and a column oven (Knauer). Radioactive peaks were resolved on a 5-μm Hypersil ODS column (4.6-mm internal diameter × 125-mm column, with a 20-mm guard column; Knauer) by gradient elution at 28°C. The mobile phase consisted of 1% ammonium formate solution, pH 6.4, and methanol. Ammonium formate was decreased from 100% (0 min) to 80% (3.1 min), 60% (21 min), and 50% (27 min). At the same time points, the methanol content was increased from 0% to 20, 40, and 50%, respectively. At 30 min, 100% methanol was used. For samples that contained only small amounts of radioactivity, 20-sec fractions of the eluent were collected using a fraction collector (Foxy; Fa. ISCO). Samples were analyzed in a liquid scintillation counter (TriCarb 2000 C-1), and data were evaluated with a Wang computer.

Protein Binding of Meloxicam. Protein binding of plasma from mice and mini-pigs was assessed using the ultrafiltration method, whereas the protein binding of rat plasma was investigated by ultraconcentration. Samples (1 ml) of mouse plasma containing radiolabeled meloxicam were transferred to the reservoirs of ultrafiltration devices (Cenfrie micropartition system; Amicon Corp., Beverly, MA). The membranes used in the devices had a molecular weight cut-off of 30,000. The devices were centrifuged at 2000g for 1 hr at 25°C in a centrifuge with a 45° fixed-angle rotor (Microrapid/K; Hettich, Tuttingen, Germany). Six ultraconcentration devices were used for each investigated plasma concentration of [14C]meloxicam (0.5, 5, and 20 μg/ml). One aliquot of the filtrate was used for radioactivity measurement and another for measurement of the protein concentration according to the method of Lowry et al. (1951). Filtrates in which the protein concentration was <0.5 mg/ml were considered acceptable for further analysis.

Protein binding in rat plasma was investigated by means of ultraconcentration (100,000g) for 16 hr, using plasma samples from animals treated with [14C]meloxicam. The level of radioactivity in the protein-poor upper layer was measured, and the protein content was estimated using the method of Lowry et al. (1951). In vivo protein binding in mini-pig plasma was quantified using plasma samples obtained from animals 4 hr after oral treatment with [14C]meloxicam, using the same experimental procedure as for mouse plasma.

Pharmacokinetic Analysis. Pharmacokinetic parameters were determined using noncompartmental methods in the TOPFIT program package (Heinzel et al., 1993). The cmax and tmax values for meloxicam were determined by direct observation of the data. The λ1 value was calculated by logarithmic-linear regression of the plasma concentration-time curve. The elimination t1/2 was calculated as 0.693 divided by λ1. The AUC to the final measurable sample was calculated using the trapezoidal rule and extrapolated to infinity, with the final plasma concentration being divided by λ1. Apparent CL/F was calculated by dividing the dose by AUC0–∞. And Vd/F was calculated by dividing the dose by the product of λ1 and AUC0–∞. MRTtot = MRTs + MRTdph was calculated according to the method of Gibaldi and Perrier (1982).

Determination of the pharmacokinetic parameters MRT, Vd/F (based on the drug concentration in plasma), Vd, and CL requires the measurement of one defined compound in plasma, which is usually performed with a chromatographic assay. In the case of meloxicam, the total radioactivity measured in plasma represents primarily the parent compound. This offers the possibility of calculating the pharmacokinetic parameters from the data on total radioactivity measured in plasma.

Animals. Rationale. Basic pharmacokinetic information was required for mice, rats, and mini-pigs, because these species were used in toxicological studies. Rats were of primary interest because they were also used extensively in pharmacological studies. The pharmacokinetics in dogs were determined to provide dosing recommendations for clinical use. The studies in baboons were undertaken to obtain data from primates, which are close to humans.

Mice. All studies were carried out with male and female albino mice (Naval Medical Research Institute [NMRI]; body weight, 21–29 g). After a 16-hr fast, a single 10 mg/kg dose of [14C]meloxicam was administered orally to male and female mice or iv to male mice only, to determine meloxicam plasma levels, urinary excretion, metabolic profiles, and protein binding. The animals were housed in metabolism cages (five mice/cage), and the excreta were collected up to 48 hr after the dose.

Rats. The majority of the animal studies of meloxicam pharmacokinetics were conducted with male and female albino rats (Specific pathogen-free [Spf], Chbb: Thom strain from Dr. Karl Thomae GmbH, Biberach, Germany; body weight, 200–250 g). After a fast of approximately 20 hr, a single dose of [14C]meloxicam was administered orally or iv, at 0.3–5 mg/kg. Tissue distribution of meloxicam was also measured in female natural gray rats (homogenous fatty [fafa] from Ifla Credo, L’Arbresle, France) and male black hooded rats (Strain Harlan Ola: Lister Hooded, Borchten, Germany) after dissection of the animals. Experiments for measuring blood levels and excretion balances were conducted with four or five animals, whereas one animal per time point was used for the autoradiographic studies.

Dogs. An open, three-way, crossover study was conducted with three male and three female beagle dogs (Chbb beagle; body weight, 11.7–13.8 kg). Single iv, oral, or sc doses of [14C]meloxicam (0.2 mg/kg) were administered 30 min after a standard meal (300-g pellets and two spoonfuls of meat). The wash-out period was 2 weeks. Blood samples were collected up to 96 hr after the dose. The parent compound in plasma was quantified using HPLC.

Mini-pigs. An initial open, two-way, crossover study was conducted with four male mini-pigs (body weight, 13–18 kg) obtained from the Royal Veterinary College (London, UK). After an overnight fast, the mini-pigs received a single oral or iv dose of [14C]meloxicam (10 mg/kg), and the plasma concentration and excretion balance of total radioactivity were measured. A subsequent study, conducted with one male and one female Göttingen mini-pig (body weight, 13 kg), investigated the tissue distribution, protein binding, and metabolic pattern of a single oral dose of [14C]meloxicam (3.5 mg/kg) administered after an overnight fast.

Baboons. Before investigation in humans, a pilot study was conducted with three baboons, to assess the pharmacokinetic profile of meloxicam in a primate species. A single dose of [14C]meloxicam at 10 mg/kg was administered by gavage. The concentration of radioactivity in plasma and the excretion balance were measured. In addition, the metabolic profiles in plasma and urine were determined.

Results

Mice. The complete pharmacokinetic profile of [14C]meloxicam in male and female mice is shown in table 1. Female mice demonstrated a higher AUC, which resulted in a smaller value being calculated for CL. However, there were no significant pharmacokinetic differences between the genders. Plasma concentrations increased rapidly after oral administration of a single 10 mg/kg dose of meloxicam, with tmax values of 0.7 and 0.6 hr in male and female mice, respectively. After a single iv dose of 10 mg/kg meloxicam, an initial concentration of 36.6 mg-eq/liter was attained after 5 min, and plasma concentrations were similar to those seen after oral dosing within 1 hr. Thereafter, the iv and oral concentration-time profiles were comparable, both showing biphasic elimination between 1 and 8 hr after dosing (fig. 2). The bioavailability (calculated as AUCoral/AUCiv) was 94%.
The elimination $t_{1/2}$ in males was relatively short (4.8 and 6.4 hr after oral and iv dosing, respectively), compared with those observed in rats, dogs, and mini-pigs (tables 2–5). Females demonstrated a $t_{1/2}$ comparable to that of males. Thus, the radioactivity resulting from a single dose was almost completely eliminated within 24 hr. The radioactivity was excreted by renal and biliary routes, with 60–65% being eliminated in urine and 35–40% being eliminated in feces. The highest tissue concentrations of radioactivity after administration of $[14\text{C}]$meloxicam (0.5 mg/kg) was high in both male and female animals (99.5–99.7%). However, the 5'-carboxy metabolite accounted for only 4.5%. In vitro protein binding was 96.8% over the range of 0.5–20.0 µg/ml $[14\text{C}]$meloxicam.

**Rats. Absorption/Pharmacokinetics.** Based on urinary $^{14}\text{C}$ excretion data, oral absorption was ~95%. Because the enolic hydroxyl group confers acid properties on meloxicam, the absorption may vary along the gastrointestinal tract because of the changing pH of the environment. However, administration of $[14\text{C}]$meloxicam (1 mg/kg) directly into the stomach, duodenum, ileum, and colon of male rats resulted in biliary excretion of 4, 6, 7, and 12% of the administered radioactivity, respectively, after 6 hr. Therefore, it appears that meloxicam is absorbed over a relatively long section of the gastrointestinal tract.

After iv administration of $[14\text{C}]$meloxicam (1 mg/kg), the radioactivity was eliminated from the blood of male and female rats in a biphasic manner (fig. 3). Although blood concentrations were virtually identical in male and female rats during the initial distribution phase, a clear gender difference emerged during the longer elimination phase, with females demonstrating considerably higher concentrations, resulting from a slower rate of elimination. A comparison of mean pharmacokinetic parameters after administration of single iv or oral doses of $[14\text{C}]$meloxicam to male and female albino rats is given in table 2. The $t_{1/2}$ was 13 hr for males and 37 hr for females. The MRT$_{tot}$ values were also different, i.e., 18 hr in males and 53 hr in females.

These gender-specific differences in the time course and concentrations of radioactivity in the blood were also observed after oral administration of $[14\text{C}]$meloxicam (fig. 4). However, because of great variation in one male rat, the value for $t_{1/2}$ was not significantly different between genders, being 50 for males and 52 hr for females. The MRT$_{tot}$ after an oral dose was 32 hr in males and 53 hr in females. Multiple oral dosing (0.3 or 1 mg/kg/day for 11 days) also revealed gender differences (table 3), with steady-state plasma concentrations being different between genders, being 50 for males and 52 hr for females.

More than 90% of radioactivity in the blood was located in the plasma and <$10\%$ was associated with erythrocytes at 2, 8, and 24 hr after oral administration of $[14\text{C}]$meloxicam. Protein binding after oral administration of $[14\text{C}]$meloxicam (0.5 mg/kg) was high in both male and female animals (99.5–99.7%). However, the 5'-carboxy metabolite of meloxicam did not displace the parent compound from its protein-bound state.

**Distribution.** The highest tissue concentrations of radioactivity after either oral (5 mg/kg) or iv (1 mg/kg) dosing were found in the liver; these concentrations were similar to those measured in blood. Whole-body autoradiographs from pigmented rats after orally administered $[14\text{C}]$meloxicam revealed moderate levels of radioactivity in the kidneys, skin, lungs, and intestinal tract but very low concentrations in skeletal muscle and the central nervous system (fig. 6). There was no specific affinity for the pigmented layers of the skin. Also, no affinity was seen for the pigmented layer of the eye. The concentrations and rates of elimination observed in these tissues were similar to those found in the lung.

**TABLE 1**

Mean pharmacokinetic parameters for total radioactivity after oral or iv administration of 10 mg/kg $[14\text{C}]$meloxicam to male and female mice (N = 5 for each time point for blood sampling).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0\rightarrow t}$</td>
<td>mg-eq/hr/liter</td>
<td>66.1</td>
<td>67.5</td>
</tr>
<tr>
<td>MRT$_{tot}$</td>
<td>hr</td>
<td>3.01</td>
<td>3.9</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>hr</td>
<td>6.12</td>
<td>4.4</td>
</tr>
<tr>
<td>$V_z$</td>
<td>liters/kg</td>
<td>1.43</td>
<td>1.13</td>
</tr>
<tr>
<td>$V_x$</td>
<td>liters/kg</td>
<td>0.467</td>
<td>0.718</td>
</tr>
<tr>
<td>CL</td>
<td>liters/hr/kg</td>
<td>0.155</td>
<td>0.164</td>
</tr>
</tbody>
</table>

**TABLE 2**

Pharmacokinetic parameters [mean and coefficient of variation (CV)] for total radioactivity after oral or iv administration of 1.0 mg/kg $[14\text{C}]$meloxicam to male and female albino rats (N = 5).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Male Mean CV</th>
<th>Female Mean CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0\rightarrow t}$</td>
<td>mg-eq/hr/liter</td>
<td>70.9 27.2</td>
<td>217 22.2</td>
</tr>
<tr>
<td>MRT$_{tot}$</td>
<td>hr</td>
<td>18.0 24.0</td>
<td>52.6 22.6</td>
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<td>$t_{1/2}$</td>
<td>hr</td>
<td>13.4 21.5</td>
<td>36.8 22.2</td>
</tr>
<tr>
<td>$V_z$</td>
<td>liters/kg</td>
<td>0.277 9.13</td>
<td>0.247 8.03</td>
</tr>
<tr>
<td>$V_x$</td>
<td>liters/kg</td>
<td>0.257 6.38</td>
<td>0.244 8.04</td>
</tr>
<tr>
<td>CL</td>
<td>liters/hr/kg</td>
<td>0.015 30.7</td>
<td>0.005 31.0</td>
</tr>
</tbody>
</table>

**Fig. 2.** Mean ± SE plasma concentration-time profiles for total radioactivity after oral or iv administration of $[14\text{C}]$meloxicam (10 mg/kg) to male mice.

Because blood could only be taken once from each mouse (because of the small volumes available), each time point is the mean from five individual mice.
mg/kg/day for 5 days) was also quantitatively investigated in male and female black hooded rats. Steady-state conditions were achieved by the third dose in both genders. The blood concentrations of radioactivity in this species were considerably lower than those seen in albino rats, because of faster metabolism and elimination. Nevertheless, the metabolite profiles in the two species were identical. Again, the highest concentrations of radioactivity were detected in the blood, liver, and kidneys, with low levels in the brain (2–3% of those found in plasma). Only low concentrations were found in the pigmented and nonpigmented areas of the skin, and none was seen in the pigmented regions of the eye. Thus, \([14C]meloxicam\) appears to have no special affinity for melanin pigment.

Studies conducted with pregnant rats investigated the transfer of meloxicam through the placenta. After a single oral dose of \([14C]meloxicam\) (5 mg/kg) on day 18 of pregnancy, the concentrations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Mean</th>
<th>CV</th>
<th>Mean</th>
<th>CV</th>
<th>Mean</th>
<th>CV</th>
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<th>CV</th>
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<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>mg/liter</td>
<td>6.4</td>
<td>12.0</td>
<td>7.50</td>
<td>18.8</td>
<td>1.48</td>
<td>49.9</td>
<td>2.44</td>
<td>14.0</td>
</tr>
<tr>
<td>(t_{\text{max}})</td>
<td>hr</td>
<td>4.19</td>
<td>35.7</td>
<td>13.1</td>
<td>23.3</td>
<td>5.20</td>
<td>47.0</td>
<td>8.31</td>
<td>28.2</td>
</tr>
<tr>
<td>(\text{AUC}_{0-\infty})</td>
<td>mg/hr/liter</td>
<td>172</td>
<td>33.3</td>
<td>437</td>
<td>20.8</td>
<td>38.8</td>
<td>61.1</td>
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</tr>
<tr>
<td>(\text{MRT}_{\text{tot}})</td>
<td>hr</td>
<td>24.0</td>
<td>35.0</td>
<td>48.6</td>
<td>9.77</td>
<td>20.7</td>
<td>24.9</td>
<td>55.8</td>
<td>28.6</td>
</tr>
<tr>
<td>(V_{i/P})</td>
<td>liters/kg</td>
<td>0.129</td>
<td>16.6</td>
<td>0.101</td>
<td>22.5</td>
<td>0.286</td>
<td>111</td>
<td>0.106</td>
<td>11.1</td>
</tr>
<tr>
<td>(CL/F)</td>
<td>liters/hr/kg</td>
<td>0.007</td>
<td>36.2</td>
<td>0.002</td>
<td>26.5</td>
<td>0.018</td>
<td>122</td>
<td>0.002</td>
<td>34.2</td>
</tr>
</tbody>
</table>

\(\text{AUC}_{\text{sp}}\), apparent volume of distribution in the central compartment.

### TABLE 4
Pharmacokinetic parameters [mean and coefficient of variation (CV)] for parent compound after iv, oral, or sc administration of 0.2 mg/kg meloxicam to male and female beagle dogs (N = 6)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Intravenous</th>
<th>Oral</th>
<th>Subcutaneous</th>
<th>Mean</th>
<th>CV</th>
<th>Mean</th>
<th>CV</th>
<th>Mean</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>mg/liter</td>
<td>0.464</td>
<td>12.7</td>
<td>0.734</td>
<td>15.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t_{\text{max}})</td>
<td>hr</td>
<td>7.5</td>
<td>110</td>
<td>241</td>
<td>16.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{AUC}_{0-\infty})</td>
<td>mg/hr/liter</td>
<td>22.9</td>
<td>16.0</td>
<td>24.1</td>
<td>13.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{MRT}_{\text{tot}})</td>
<td>hr</td>
<td>40.0</td>
<td>21.9</td>
<td>35.0</td>
<td>13.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_z)</td>
<td>liters/kg</td>
<td>0.32</td>
<td>20.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CL)</td>
<td>liters/hr/kg</td>
<td>0.009</td>
<td>14.7</td>
<td>0.038</td>
<td>17.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\text{AUC}_{\text{sp}}\), AUC from the last measurable sample to infinity.

### TABLE 5
Pharmacokinetic parameters [mean and coefficient of variation (CV)] for total radioactivity after oral or iv administration of 10 mg/kg \([14C]\)meloxicam to male mini-pigs (N = 3)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Intra</th>
<th>Oral</th>
<th>Mean</th>
<th>CV</th>
<th>Mean</th>
<th>CV</th>
<th>Mean</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>mg-eq/liter</td>
<td>15.35</td>
<td>21.8</td>
<td>243</td>
<td>14.5</td>
<td>243</td>
<td>14.5</td>
<td>214</td>
<td>14.5</td>
</tr>
<tr>
<td>(t_{\text{max}})</td>
<td>hr</td>
<td>3.0</td>
<td>57.7</td>
<td>7.0</td>
<td>10.3</td>
<td>7.3</td>
<td>10.3</td>
<td>7.3</td>
<td>10.3</td>
</tr>
<tr>
<td>(\text{AUC}_{0-\infty})</td>
<td>mg-eq/hr/liter</td>
<td>24.9</td>
<td>14.5</td>
<td>214</td>
<td>14.5</td>
<td>214</td>
<td>14.5</td>
<td>214</td>
<td>14.5</td>
</tr>
<tr>
<td>(\text{MRT}_{\text{tot}})</td>
<td>hr</td>
<td>67.4</td>
<td>34.1</td>
<td>67.5</td>
<td>27.5</td>
<td>67.5</td>
<td>27.5</td>
<td>67.5</td>
<td>27.5</td>
</tr>
<tr>
<td>(V_{i/P})</td>
<td>liters/kg</td>
<td>7.38</td>
<td>17.8</td>
<td>9.85</td>
<td>23.9</td>
<td>9.85</td>
<td>23.9</td>
<td>9.85</td>
<td>23.9</td>
</tr>
<tr>
<td>(CL)</td>
<td>liters/hr/kg</td>
<td>0.043</td>
<td>22.0</td>
<td>0.047</td>
<td>15.5</td>
<td>0.047</td>
<td>15.5</td>
<td>0.047</td>
<td>15.5</td>
</tr>
</tbody>
</table>
of radioactivity in the livers of the mothers were about 3–5 times greater than those in fetal livers, and the levels in the placenta were about one half those in maternal blood. The levels in fetal skeletal muscle were somewhat higher than those in maternal skeletal muscle.

In male rats with antigen (*Mycobacterium butyricum*)-induced arthritis of the hind paws, multiple oral doses of meloxicam (0.5 mg/kg/day for 19 days) followed by [14C]meloxicam (5 mg/kg/day for 2 days) resulted in marked distribution of radioactivity in the chronically inflamed tissues; negligible radioactivity was detected in the noninflamed front paws. Thus, despite the relatively poor blood supply to these tissues, meloxicam was distributed preferentially into sites of inflammation, probably because of the lower pH in those areas (Busch and Engelhardt, 1990).

**Elimination.** After id or iv administration of [14C]meloxicam (1 mg/kg) to anesthetized male rats, elimination in the bile accounted for approximately 10% of the dose within 6 hr, with the value being somewhat lower with id than with iv dosing. Similarly, 10–12% of the radioactivity was excreted via the biliary route after id administration of radioactive bile taken from a donor animal (enterohepatic circulation). As observed with blood levels of radioactivity, there were considerable differences between male and female rats. During the first 6 hr after id administration of [14C]meloxicam (1 mg/kg), the rate of biliary excretion in male rats was almost twice that in females (7.9% vs. 4.2%).

Renal excretion was the main route of elimination in rats, accounting for approximately 70% of the orally or iv administered [14C]meloxicam dose (1 mg/kg). The remainder of the dose was eliminated in the feces. In males, only 8% of the dose remained in the body after 72 hr, and elimination was complete after 96 hr. In accordance with the higher blood concentrations seen in females, the radioactivity was excreted more slowly; 72 hr after oral dosing (and 96 hr after iv dosing), 30% of the dose remained in the body.

Elimination in lactated milk was studied in rats nursing 9–11-day-old pups. Oral administration of [14C]meloxicam (5 mg/kg) resulted in higher concentrations of radioactivity in milk than in plasma at 5 hr (22.3 vs. 18.4 mg/liter) and 24 hr (9.9 vs. 6.0 mg/liter) after dosing. One hour after dosing, the levels were somewhat higher in plasma than in milk (12.6 vs. 9.7 mg/liter). Sixty to 70% of radioactivity in the milk was associated with the unchanged parent compound.

**Metabolite Profile and Pharmacokinetics of the Main Metabolites.** Investigation of the metabolite profile revealed that the parent compound accounted for approximately 85% of the radioactivity present in the plasma after oral or iv dosing with [14C]meloxicam (1 mg/kg). In contrast, only traces of the radioactivity in the urine were accounted for by the parent compound, with the majority being due to three polar metabolites, *i.e.* the 5'-carboxy metabolite (acid metabolite) and the 5'-hydroxymethyl metabolite (alcohol metabolite), both of which were formed by oxidation of the methyl group in the thiazolyl ring, and a third metabolite formed by cleavage of the side chain (Schmid *et al.*, 1995b). A number of gender-specific differences were noted in the concentrations, but not the profiles, of metabolites. Most markedly, female rats eliminated only 30% of the amount of the 5'-carboxy metabolite eliminated by male rats. A number of minor gender-specific differences were also observed in the metabolite profiles in bile; the principal metabolite for both genders was the 5'-carboxy metabolite.

The pharmacokinetic characteristics of the principal metabolites of meloxicam were assessed after oral or iv administration of two [14C]-labeled metabolites (5'-hydroxymethyl and 5'-carboxy metabolites, 1 mg/kg) to male rats. Although neither metabolite is associated with biological activity at pharmacologically relevant doses (Engelhardt and Trumlitz, 1990), their pharmacokinetic profiles differed markedly from that of the parent compound. Peak blood concentrations were attained within 0.4–0.7 hr after oral dosing, and the extents of absorption were 57% for the 5'-hydroxymethyl metabolite and 14% for the 5'-carboxy metabolite. In addition, both metabolites were rapidly eliminated so that, by 8 hr after administration, only 0.2–0.5% of Cmax remained in the blood after iv dosing and 4–16% remained after oral dosing.

**Dogs.** The mean plasma concentration-time profiles of the parent compound after iv, oral, or sc administration of 0.2 mg/kg meloxicam to dogs are shown in fig. 7. The sc route of administration was chosen because this was the parenteral route of dosing intended for the therapeutic treatment of osteoarthritis in dogs. The pharmacokinetic profile of meloxicam in dogs is shown in table 4. Values for t1/2, AUC0–∞, AUC to the final measurable sample, CL/F, and V/F were

![Fig. 5. Mean ± SE plasma concentration-time profiles for meloxicam after multiple oral administration (11 times) of meloxicam (4 mg/kg) to male (N = 8) and female (N = 8) rats.](image1)

![Fig. 6. Tissue distribution in a female natural gray rat 5 hr after oral administration of 5 mg/kg meloxicam (N = 1).](image2)

![Fig. 7. Mean ± SD plasma concentration-time profiles for 96 hr (main figure) or 24 hr (inset) for meloxicam after iv, oral, or sc administration of meloxicam (0.2 mg/kg) to dogs (N = 6).](image3)
comparable for all routes of administration. The absorption kinetics of meloxicam, i.e. \( C_{\text{max}} \) and \( t_{\text{max}} \), showed marked differences between the oral and sc routes. This was expected because of the different pharmaceutical formulations used and because of the difference in absorption of the compound in the gastrointestinal tract and the sc layer of the skin. Values for \( t_{\text{max}} \) were higher after oral dosing, compared with sc dosing (7.5 vs. 2.5 hr), whereas \( C_{\text{max}} \) was higher after sc dosing (0.734 vs. 0.464 mg/liter). Because of this difference in absorption, the MRT was also somewhat higher after oral dosing.

Despite a relatively wide range of \( t_{1/2} \) values, the mean value of 24 hr was within the range seen for male and female rats. However, in contrast to the results obtained with rats, female dogs showed a trend toward lower AUC and \( t_{1/2} \) values (data not shown).

A compartmental analysis using the TOPFIT program (Heinzel et al., 1993) was performed to predict the time curve of plasma concentrations after repeated daily oral dosing. Simulation of plasma-time profiles revealed an accumulation factor of 2.1–3.3, and thus steady-state conditions would be reached after three to five doses, using a dosing interval of 24 hr. Because \( C_{\text{max}} \) was achieved earlier after sc dosing (0.734 vs. 0.464 mg/liter), the MRT was also somewhat higher after oral dosing.

Complete absorption was demonstrated for both the oral and sc routes, with absolute bioavailability values of 106 and 112%, respectively. Therefore, the two routes should be associated with similar therapeutic efficacies.

Plasma protein binding data showed that 97% of [\( ^{14} \text{C} \)] meloxicam was bound to plasma proteins. The level of unbound, pharmacodynamically active meloxicam is therefore about 10 times higher than that determined in rats, after a dose of 0.2 mg/kg in each species.

**Mini-pigs.** The plasma concentration-time profiles of total radioactivity after oral or iv administration of [\( ^{14} \text{C} \)] meloxicam to male mini-pigs are shown in fig. 8. The pharmacokinetic parameters resulting from noncompartmental analysis of the plasma radioactivity levels are given in table 5. The \( t_{\text{max}} \) after oral administration was 3 hr; the long terminal elimination \( t_{1/2} \) for total radioactivity of about 145 hr was the result of the presence of metabolites in plasma. By measuring only the parent compound in plasma, a terminal \( t_{1/2} \) of about 8 hr was estimated (but not shown in table 5); this is the most relevant \( t_{1/2} \) value.

Excretion studies over 5 days showed approximately 87% recovery of the total radioactivity administered either orally or iv. After oral administration, about 34% of the dose was excreted in the urine and 46% in the feces; radioactivity in the debris and washings from the cages accounted for approximately 7% of the dose. Values obtained after iv dosing were 39% in urine, 44% in feces, and 4% in cage washings. Thus, both renal and biliary excretion are important routes of elimination in this species.

**Investigation of the metabolite profile of meloxicam** indicated that the majority of radioactivity circulating in plasma up to 12 hr after oral or iv dosing was accounted for by the unchanged parent compound (approximately 70–80% up to 6 hr and 60–70% from 6 to 12 hr). However, the parent compound accounted for only 1% of the total radioactivity in the urine up to 24 hr after oral or iv dosing and 17% of the total radioactivity in the feces up to 48 hr after oral administration. The level of the parent compound in feces after iv dosing was below the limit of detection. The parent compound in feces after oral dosing probably represented nonabsorbed meloxicam. Enzyme treatments (\( \beta \)-glucuronidase and arylsulfatase) had no effect on the pattern of the parent compound or the two metabolites detected in the urine, indicating a lack of phase II metabolism for meloxicam in pigs.

In a study investigating the metabolism of meloxicam in two Göttingen mini-pigs, the \( 5' \)-hydroxymethyl and \( 5' \)-carboxy metabolites were identified as the main metabolites after oral dosing. This result is similar to the finding in rats. The majority of radioactivity in the urine samples was associated with the \( 5' \)-hydroxymethyl metabolite (about 50%), whereas the \( 5' \)-carboxy metabolite accounted for 10% of the radioactivity. In contrast, in bile the \( 5' \)-carboxy metabolite accounted for the majority of the radioactivity (56% in the male and 97% in the female), whereas the \( 5' \)-hydroxymethyl metabolite accounted for 34% of the radioactivity in the male but only 2% of the radioactivity in the female mini-pig. As expected from previous studies, the majority (82–93%) of the radioactivity circulating in the plasma of both genders was from the unchanged parent compound.

The study of the two Göttingen mini-pigs was performed to determine the distribution of radioactivity in tissues, because mini-pigs serve as a nonrodent species in toxicological studies. The total overall recovery of radioactivity 4 hr after dosing was 82% in the male animal and 71% in the female. Absorption was incomplete in the female at 4 hr, as shown by the relatively high percentage of radioactivity still present in the stomach contents and in the stomach wall. The highest tissue concentrations of radioactivity were found in the liver (3–4%) and kidneys (1%), probably because of the excretory functions of these organs, and relatively high levels were also seen in skin, bone, and cartilage. As previously observed in rats, only low levels were found in the eye and brain. The plasma/tissue ratio was high throughout, indicating a low volume of distribution. The highest percentage of radioactivity was found in urine in the bladder (32% in the male and 17% in the female), whereas the feces in the large intestine accounted for 9% and 2%, respectively.
Plasma protein binding in vitro was calculated to be approximately 96%. This value is lower than that reported in rats and may account for the higher rate of meloxicam elimination seen in mini-pigs.

**Baboons.** After oral administration of [14C]meloxicam to baboons, mean peak plasma concentrations of radioactivity were attained after approximately 6 hr, and the majority of the radioactivity was eliminated within 24 hr (table 6). By 72 hr after dosing, elimination was virtually complete. The elimination $t_{1/2}$ for total radioactivity was 6 hr. As seen in other animal species, the majority of the radioactivity was found in the plasma, rather than the erythrocytes.

Approximately one third (35%) of the dose was excreted in the urine and 42% was excreted in the feces. Because no reliable information was obtained for the remaining 23% in cage washes and cage debris, the predominant route of excretion in primates could not be determined. Urinary excretion was nearly complete within 24 hr of administration, with 29% of the dose being eliminated within this period and only 6% being excreted in the subsequent 72 hr. Excretion via the fecal route was almost complete within 24 hr of dosing.

Only the parent compound was found in the plasma, whereas meloxicam represented a small proportion (4%) of the total radioactivity in the urine. Five polar metabolites were found in the urine; three of them accounted for 75% of the total radioactivity. The $t_{1/2}$ of elimination was about 3 times shorter than that in humans. Therefore, baboons were not used for further investigations.

**Discussion**

The studies described here with rats, mice, dogs, mini-pigs, and baboons have provided a survey of the pharmacokinetics of meloxicam in animals. Meloxicam was well absorbed in all species.

A relatively high, persistent concentration of total radioactivity in plasma, followed by a slow decrease, was observed in rats, with a $t_{1/2}$ of 13–15 hr. After iv administration, the disposition pharmacokinetic parameters were similar to values in humans (table 7). This was confirmed by inspection of the plasma concentration-time curves for both species (Schmid et al., 1995a; Türck et al., 1996). Meloxicam circulated nearly exclusively as the parent compound in the plasma of humans, rats, mice, dogs, and baboons (for data for mini-pigs, see below). For humans and rats, pharmacokinetic parameters evaluated from measurements of total radioactivity and parent compound levels were therefore rather similar. (The long elimination $t_{1/2}$ of about 50 hr for total radioactivity seen in male rats after single oral dosing was the result of large individual variations in this particular study and is not representative.)

The profile in mice after administration of the radiolabeled compound differed markedly from that in rats, with a shorter elimination $t_{1/2}$ and lower total exposure to the drug (AUC). The free compound can be considered a relevant parameter for pharmacodynamics, and mice demonstrated an AUC value comparable to that of rats and humans with respect to free compound, because the percentage of protein binding in mice, dogs, and mini-pigs (96–97%) was relatively low, compared with that found in rats (99.7%) and humans (>99.5%) (Schmid et al., 1995a).

Mini-pigs demonstrated a short elimination $t_{1/2}$ of 8 hr for the parent compound. Interestingly, the elimination $t_{1/2}$ of the metabolites was very long (~145 hr). This finding was not observed in any other species. In baboons, the elimination $t_{1/2}$ for the elimination of total radioactivity from plasma was shorter than in humans.

In particular, rats demonstrated gender-specific differences in the plasma levels of parent compound, with greater total exposure to drug and greater MRT and elimination $t_{1/2}$ values in females than in males. These differences were less marked in mice. In dogs, the mean elimination $t_{1/2}$ was comparable to that previously reported for rats. However, in contrast to the results obtained with mice and rats, female dogs showed a trend toward lower total exposure to drug and lower elimination $t_{1/2}$ values, compared with male dogs, although there was a wide range of individual values.

Meloxicam is cleared almost exclusively metabolically, because only low levels of parent compound were detected in bile, urine, and feces. Therefore, biotransformation governs the elimination of parent compound in all species. The main metabolites of meloxicam in humans, rats, mice, and mini-pigs were a 5'-hydroxymethyl derivative and a 5'-carboxy derivative. Other metabolites have also been detected in rats and humans (Schmid et al., 1995a,b); the major metabolite is (5-methyl-2-thiazolyl)aminooxoaetic acid, which is typical for oxicams (Woolf and Rudalovic, 1989).

The observation of a gender difference in rats fits very well with our knowledge of the enzymatic basis of the biotransformation of meloxicam. In humans (Chesne et al., 1996, 1998), the formation of the primary 5'-hydroxymethyl metabolite was studied in detail. This metabolite is formed by two CYPs, with different affinities; CYP2C9 is the more important component at physiological concentrations ($K_M$ ~ 10 µM, $V_{max}$ ~ 8 pmol/min/mg protein) and CYP3A4 is less significant ($K_M$ ~ 475 µM, $V_{max}$ ~ 23 pmol/min/mg protein). CYP2C11 and CYP2C7 are important members of the CYP2C family in rats (Funae and Imaoka, 1993; Ryan and Levin, 1993). CYP2C7 is expressed in both genders; CYP2C11, however, is more important in male rats. It has approximately 80% sequence homology to human CYP2C9. The absence of CYP2C11 in females may explain the longer elimination $t_{1/2}$. Certainly, the activity of drug-metabolizing enzymes decreases with age because of changes in CYP levels, most notably the gender-specific forms of CYP (Funae and Imaoka, 1993; Ryan and Levin, 1993; Soucek and Gut, 1992).

Studies conducted in rats and mini-pigs revealed the highest tissue concentrations of meloxicam to be in the liver, kidneys, and lungs, with low levels in the central nervous system. Meloxicam and its metabolites showed no affinity for pigmented tissue. However, transfer of meloxicam into the placenta and into lactated milk was clearly demonstrated in rats. Elimination of total meloxicam radioactivity was complete after 96 hr in male rats, whereas, in accordance with their higher blood concentrations, females excreted total radioactivity over a longer period, a finding that has also been reported for piroxicam.


