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Dermal absorption and disposition of musk ambrette, musk ketone and musk xylene in rats

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Abstract

Dermal doses of carbon-14 labelled musk ambrette (MA), musk ketone (MK) or musk xylene (MX) to male Sprague–Dawley CD rats were applied at a nominal dose level of 0.5 mg/kg (11 μg/cm^2 of skin) and excess material removed at 6 h. Means of about 40, 31 and 19% of the applied doses of MA, MK and MX, respectively, were absorbed. Most of the absorbed material was excreted within 5 days with only 1–2% of the applied dose remaining in the animal at this time. Tissue concentrations of radiolabel were similar for all three compounds with peak concentrations occurring at 6–8 h. In general, fat and liver contained the highest concentrations at around 0.2 μg nitromusk equivalents/g but concentrations in fat declined fairly rapidly to around 0.005 μg equiv./g at 120 h. Most of the absorbed dose was eliminated in bile mainly in the form of polar conjugated metabolites. Structural characterisation of the major aglycones for MA and MX indicated that they were hydroxylated analogues formed by oxidation of the ring methyl. Repeated daily dosing for 14 days resulted in little bioaccumulation for musk xylene and accumulation of about three-fold for musk ketone. © 1999 Published by Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Musk ambrette; Musk ketone; Musk xylene; Dermal absorption; Rat

1. Introduction

Five nitroaromatic compounds, known as the nitromusks, are or have been used as fragrance ingredients (Ford, 1998). Three of these compounds, musk ambrette, musk ketone and musk xylene, were at one time the most important fragrance ingredients in this group. Musk ambrette was withdrawn from use due primarily to its rare but well confirmed photosensitization effect in humans (Cronin, 1984). It is also known to cause neurotoxic and reproductive effects in rats, albeit at high dose levels (Spencer et al., 1984). Musk xylene and musk ketone continue to be important fragrance ingredients and do not cause such effects in rats (Ford et al., 1990) or in humans (Cronin, 1984).

In 90-day dermal studies, musk xylene caused increased liver weights, with no accompanying

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histopathology, at the highest dose but no other significant effects (Ford et al., 1990). Musk xylene has been shown to cause an increase in hepatocellular adenomas and carcinomas in the diet of B6C3F1 mice for 2 years (Maekawa et al., 1990) however, there is convincing evidence that musk xylene has no genotoxic potential (Api et al., 1995; Enig et al., 1996; Kevekordes et al., 1996; Mersch-Sundermann et al., 1996; Kevekordes et al., 1997). Further studies (Thatcher and Caldwell, 1994; Caudill et al., 1995; Lehman-McKeeman et al., 1995, 1997) have shown that musk xylene is a weak inducer of CYP1A2 and a more significant inducer of CYP2B enzymes in the B6C3F1 mouse, indicating that musk xylene acts in a manner similar to phenobarbital and should be considered as a non-genotoxic murine carcinogen.

Musk ketone has not been studied in long-term studies but has been shown to increase liver weight with no accompanying histopathology in a 90-day dermal study (Ford et al., 1990). It has also been shown to have no genotoxic potential (Api et al., 1996).

Musk xylene and musk ketone have also been found in human breast milk and in human fat samples (Liebl and Ehrenstorfer, 1993; Rimkus and Wolf, 1993; Rimkus et al., 1994; Müller et al., 1996) presumably as a result of absorption through the skin after the use of fragranced consumer products.

In vitro dermal absorption studies showed that less than 6% of musk ketone and less than 2% of musk xylene is absorbed through full thickness rat skin under occlusion over 24 h (Ashcroft and Hotchkiss, 1996). However, others have reported higher amounts with musk xylene both on guinea pig skin, 55% from an emulsion vehicle and 45% from a methanol vehicle, and on human skin, 22% for both vehicles (Hood et al., 1996).

Thus, studies were initiated to evaluate dermal absorption, excretion and metabolism in laboratory animals as well as to provide the information necessary to perform investigations into the systemic exposure in human volunteers. It was also decided to investigate the potential for bioaccumulation in the rat by daily repeated dermal application.

The metabolism of musk xylene has been studied in the rat after oral administration (Minegishi et al., 1991) where both reduction of a nitro group to an amine and hydroxylation of methyl groups were observed. Additionally, significant biliary excretion was reported. No studies are available for the nitromusks by the more relevant route of dermal application. Thus, an attempt was made to identify the principle biliary metabolites after dermal application.

To provide required data to support the planned studies with human subjects, the above studies were conducted in two species of rat, the Sprague–Dawley CD and the Long Evans.

2. Materials and methods

2.1. Chemicals

Samples of the nitromusks were obtained from the following sources, musk ambrette and musk ketone (Haarmann & Reimer GmbH, Germany) and musk xylene (Bush Boake Allen Ltd., UK). Samples of each compound uniformly labelled with carbon-14 in the ring were synthesised at Huntingdon Research Centre with radiochemical purities of greater than 98% and specific activities of 31.21–37.25 mCi/mmol. All other chemicals were of reagent grade or better.

2.2. Animals

Adult male rats (16 Sprague–Dawley CD and 5 Long Evans) bodyweight about 200 g and aged 6 weeks were obtained from Charles River (Margate, Kent, UK). Animals were provided with food Laboratory Diet No.1 (Spratt's Ltd., Barking, UK) and water at all times and identified by markings on the tail. All rats were housed individually in glass metabolism cages for the duration of the studies.

2.3. Dermal absorption studies

Each compound was applied to the backs of the animals, which were shaved over an area of 16 cm^2. The ^{14}C-compound was formulated in a mix-

ture of ethanol and phenylethyl alcohol (minimum amount to maintain solubility — about 1%) at a concentration of 1 mg/ml and 0.1 ml applied evenly over an area of 9 cm^2 for a total dose of 0.5 mg/kg. The treated area was covered with aluminium foil and Sleek® waterproof dressing (Smith & Nephew Pharmaceuticals, Welwyn, UK). After dose application animals were housed singly in glass metabowls to facilitate the separate collection of urine and faeces. Urine was collected in solid CO_2 cooled containers at 0–6-, 6–24 and 24-h intervals thereafter for 5 days and faeces up to the time of sacrifice at 24-h intervals. After 6 h, the dressing and foil were removed and the area of treated skin wiped with cotton wool swabs containing 1% ethanolic phenylethyl alcohol. Pairs of Sprague–Dawley rats were sacrificed by cervical dislocation at 1, 3, 6, 8, 24, 48, 96 and 120 h after dosing and a sample of blood withdrawn by cardiac puncture. The Long Evans rats were killed similarly at 6, 24, 48, 96 and 120 h. The treated area of skin and various tissues were dissected from the carcass.

The bile ducts of additional Sprague–Dawley rats (two for musk ambrette and one each for musk ketone and musk xylene) were cannulated with 0-0 gauge nylon cannula, under halothane:oxygen anaesthesia immediately before dosing as described above and bile and urine collected for 18 h for musk xylene and for 24 h for musk ambrette and musk ketone.

For the repeated dose experiments, groups of eight animals were dosed daily with ^{14}C-musk xylene or ^{14}C-musk ketone as described above. The test compound was applied daily up for up to 14 days to an area of 9 cm^2 and adjusted according to daily bodyweight to provide a nominal daily dose of 0.5 mg/kg. Urine and faeces were collected for 24-h periods after 1, 2, 3, 7, 9, 11, and 13 doses or until sacrifice. Pairs of rats were sacrificed 24 h after seven doses and 6, 24 and 48 h after 14 doses. Blood samples were obtained by cardiac puncture and after sacrifice by cervical dislocation the brain, kidneys, liver, thyroid, samples of perirenal fat and the dosed skin removed from the carcass. All samples were stored at −20°C until analysed.

2.4. Sample analysis

Faeces and finely minced rat carcasses, including the bones, were separately extracted once by homogenisation in methanol. After centrifugation, samples of the extract and residue were analysed. Skin samples were digested in ethanolic potassium hydroxide. Samples of urine (1 ml), plasma (0.5 ml), solvent extracts (0.5 ml), skin digests (0.5 ml), contents of expired air traps (1 ml) and cage washings were mixed with M1-31 scintillator (Packard Instrument Company, Cavesham, UK). Samples of tissue (0.05–0.5 g) and residues of extracted carcasses (0.1–0.6 g) were combusted in oxygen using an Automatic Sample Oxidiser (Model 306, Mk2, Tri-Carb®, Packard Instrument Company). Combusted products were absorbed into Carbo-Sorb™ and mixed with Permfluor®-v scintillation system. Radioactivity was measured with a Philips Liquid Scintillation analyser (Phillips, N.V., Eindhoven, Holland). Radioactivity in amounts less than twice the background was considered to be the limit of accurate measurements.

2.5. Chromatographic analysis

Bile and urine samples were prepared by evaporation under reduced pressure or under a stream of nitrogen at 37°C and extracting the concentrate with methanol or acetone. After centrifugation, the supernatants, which contained greater than 90% of the radioactivity, were applied directly to thin-layer plates. Samples of urine and bile were incubated at 37°C for 16 h with an equal volume of 0.1 M sodium acetate buffer (pH5) and β-glucuronidase (Type H1, Sigma). Further samples were incubated with sulphatase (Sigma) in 0.1 M sodium hydrogen phosphate buffer.

Thin layer chromatography was carried out on pre-layered Kieselgel F_{254} plates (E. Merck A.G., Darmstadt, Germany) of layer thickness 0.25 mm using the following developing solvents chloroform:acetone:water (4:18:1, v/v) ethyl acetate:acetone (1:1, v/v). Radioactive components on thin-layer plates were detected either by apposition autoradiography using X-ray film or with a Berthold Mark 2 radiochromatogram scanner.

2.6. Mass spectometry

Samples of deconjugated bile were extracted twice with ethyl acetate, the extracts concentrated and applied directly to thin-layer plates. After an initial purification using chloroform:acetone:water (4:18:1, v/v) as developing solvent, metabolites were separated using hexane:ethyl acetate (6:4 v/v). Mass spectra were obtained using a VG 7070E mass spectrometer (VG Analytical, Manchester, UK). Samples were introduced by the direct insertion probe and subjected to alternate electron impact/chemical ionisation (ACE) conditions. Electron impact spectra were obtained with an electron energy of 70 eV and trap current of 200 μA and chemical ionisation spectra were obtained with an electron energy of 50 eV, an emission current of 500 μA and isobutane as the reactant gas.

3. Results

The data obtained from the Sprague–Dawley rats and the Long Evans rats were essentially identical and are combined in the following and in Tables 1–3.

Analysis of samples from animals sacrificed at 6 h indicated that while little material was excreted in urine and faeces during this time, appreciable amounts had been absorbed as assessed by the amounts of the dose in the carcass 21.8–9.8% MA > MK > MX (Tables 1–3). Most of the remaining material was on the surface of the treated skin and would have been removed from those animals maintained for longer than 6 h. At 8 h, 2 h after removal of the applied dose from the surface of the skin, means of 9.9, 8.5 and 8.4% of the dose remained in the treated skin for musk ambrette, musk ketone and musk xylene, respec-

Table 1
Fate of ^{14}C-musk ambrette after dermal application of 0.5 mg/kg to male rats[a]

Hours	1	3	6	8	24	48	96	120
Urine	NC[b]	NC	0.91	2.38*	8.54	6.15	8.45	10.7
Faeces	NC	NC	0.27*	0.86*	7.13	21.0	21.1	27.1
Carcass and tissues	3.37*	9.24*	21.8	28.4*	13.7	2.85	1.26	1.36
Total absorbed	3.37	9.24	22.98	31.6	29.4	30.0	30.8	39.2
Treated skin	90.5*	81.3*	69.4	9.95*	3.47	3.61	2.45	3.02
Dressing washings	13.1*	13.9*	10.7	58.4*	64.6	65.1	68.7	58.9
Total recovery	107	104	103	100	97.4	98.7	102	101

[a] Results are expressed at percent of applied dose and are mean of three rats at each time point except for those marked with * which are the mean of only two CD Sprague–Dawley rats.
[b] NC, sample not collected.

Table 2
Fate of ^{14}C-musk ketone after dermal application of 0.5 mg/kg to male rats[a]

Hours	1	3	6	8	24	48	96	120
Urine	NC[b]	NC	0.37	0.75*	3.73	5.97	7.93	8.47
Faeces	NC	NC	0.01	0.15*	7.60	17.3	18.7	20.5
Carcass and tissues	2.3*	10.2*	17.7	18.4*	12.9	6.13	2.37	2.10
Total absorbed	2.3	10.2	18.1	19.3	24.2	29.4	29.0	31.1
Treated skin	72.4*	66.8*	74.2	8.50*	3.30	2.47	2.63	3.63
Dressing washings	23.8*	18.3*	8.7	74.4*	76.7	69.3	71.2	68.7
Total recovery	98.5	95.2	101	102	104	101	103	103

[a] Results are expressed at percent of applied dose and are mean of three rats at each time point except for those marked with * which are the mean of only two CD Sprague–Dawley rats.
[b] NC, sample not collected.

Table 3
Fate of ^{14}C-musk xylene after dermal application of 0.5 mg/kg to male rats[a]

Hours	1	3	6	8	24	48	96	120
Urine	NC[b]	NC	0.08	0.15*	2.79	2.97	3.59	3.92
Faeces	NC	NC	<0.01	<0.01*	4.59	13.3	17.3	14.8
Carcass and tissues	0.87*	3.76*	9.82	14.6*	10.5	2.15	0.47	0.36
Total absorbed	0.87	3.76	9.90	14.7	17.8	18.5	21.4	19.1
Treated skin	81.4*	80.3*	58.0	8.41*	3.55	1.72	2.97	1.87
Dressing washings	14.2*	11.4*	23.3	70.2*	72.9	74.1	67.4	72.5
Total recovery	96.4	95.4	91.2	93.3	94.3	94.2	91.8	93.4

[a] Results are expressed at percent of applied dose and are mean of three rats at each time point except for those marked with * which are the mean of only two CD Sprague–Dawley rats.
[b] NC, sample not collected.

tively (Tables 1–3). At 120 h absorption and excretion was essentially complete. Only small amounts remained in the carcass and similar small amounts in the treated skin (2–3%). A similar pattern of excretion of absorbed material was apparent for all three compounds with the larger amount in faeces compared to urine with ratios of about 2.5:1 for musk ambrette and musk ketone and 4:1 musk xylene.

The total absorption after 120 h calculated from material excreted in urine and faeces and that retained in the carcass excluding the treated skin was 39.2% for musk ambrette, 31.1% for musk ketone and 19.1% for musk xylene. Levels in the treated skin decreased steadily after removal of the dose on the surface but did not change appreciably after 48 h.

Tissue concentrations of radioactivity were generally very low with peak levels occurring at 6–8 h (Figs. 1–3). In general, fat and liver contained the highest concentrations and levels in fat were similar for all three compounds at about 0.2 μg equiv./g. Fat concentrations declined fairly rapidly until 120 h when levels were as low as, or lower than, other tissues at around 0.005 μg equiv./g.

Experiments in bile duct cannulated rats resulted in 34 and 16% of the dermal dose of musk ambrette and musk ketone being eliminated in bile during 24 h, and during 18 h 27% of musk xylene was similarly eliminated. In all three cases, only 1 to 2% of the dose was excreted in the urine.

During 14 repeated daily doses of musk xylene and musk ketone, excretion in the faeces and urine rose from about 1.5 and 2.4% in the urine and faeces, respectively, reaching a high for musk ketone on days 9, (2.7% in the urine) and 11, (11.7% in the faeces) (Table 4). For musk ketone, the highest levels occurred on days 11, (14.9% in the faeces) and 13, (6.5% in the urine) (Table 4). For musk xylene, tissue levels at 24 h after the last of 14 daily doses only slightly exceeded those after one dose while for musk xylene the levels after 14

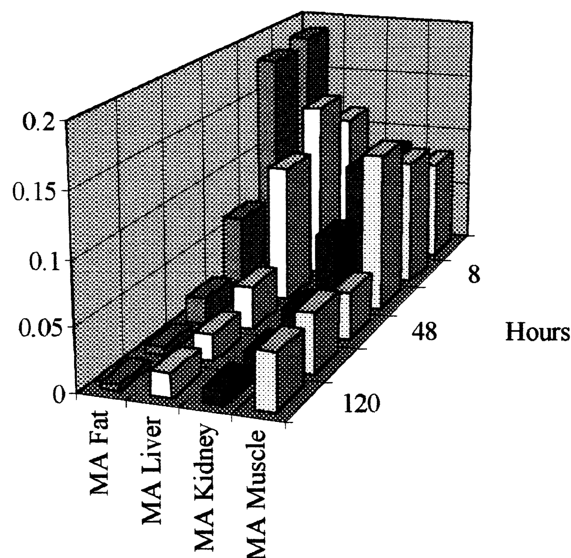

Fig. 1. Tissue concentrations of radioactivity (μg equiv./g) in male rats ($n = 2$) following a 6-h exposure to topical doses of musk ambrette.

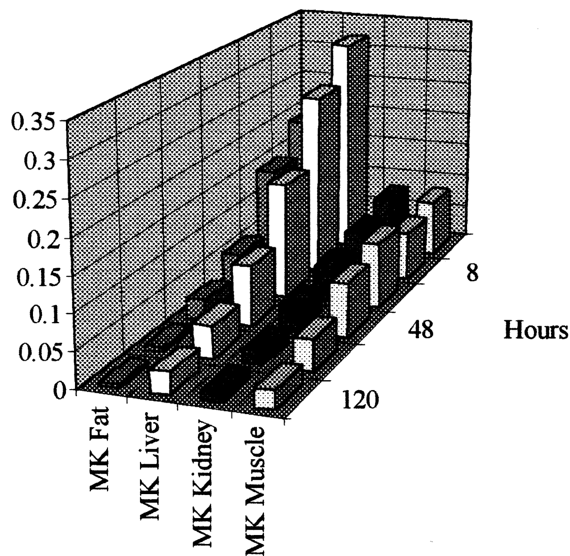

Fig. 2. Tissue concentrations of radioactivity (μg equiv./g) in male rats ($n = 2$) following a 6-h exposure to topical doses of musk ketone.

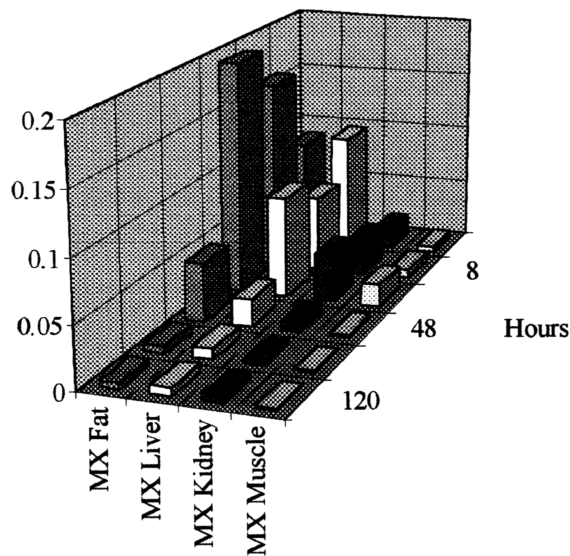

Fig. 3. Tissue concentrations of radioactivity (μg equiv./g) in male rats ($n = 2$) following a 6-h exposure to topical doses of musk xylene.

doses were approximately three-fold higher than after one dose (Table 5). For musk xylene, highest concentrations were in fat representing 0.22 μg equiv./g 24 h after the last dose. For musk ketone, highest concentrations at 24 h after the last of the 14 daily doses were in the liver representing 0.53 μg equiv./g while fat concentrations were 0.15 μg equiv./g.

In general, chromatograms of urine samples showed a complex mixture of polar metabolites. Although there was some evidence for the presence of glucuronides for musk xylene, most of the metabolites of musk ambrette and musk ketone were not simple conjugates such as glucuronides and sulphates. Further analyses were not possible due to the number of components and the small amounts.

Analysis of bile samples showed the presence of polar metabolites for all three compounds, which appeared to consist almost entirely of glucuronide conjugates. After enzyme-hydrolysis, musk ambrette samples contained a major metabolite representing about 40% of the total. Similar treatment of musk xylene samples showed the presence of one single major conjugated metabolite while musk ketone samples contained at least two major less polar metabolites.

The mass spectrum of the purified musk ambrette aglycone indicated a metabolite formed by addition of an oxygen to the parent. The loss of a fragment corresponding to a t-butyl in the electron impact indicated that the oxidation did not take place there.

Similarly, the major deconjugated metabolite of musk xylene was isolated and purified. The mass

Table 4
Excretion of radioactivity during 14 repeated daily topical doses of musk ketone and musk xylene to male rats ($n = 2$–8)[a]

Number of doses	Musk ketone		Musk xylene	
	Urine	Faeces	Urine	Faeces
1	1.42	2.42	1.48	2.34
2	1.72	9.41	2.64	5.22
3	1.73	6.62	2.67	5.70
5	1.82	7.45	3.12	8.17
7	2.09	8.77	4.37	9.55
9	2.71	9.80	5.55	12.98
11	2.10	11.70	6.10	14.85
13	2.62	11.16	6.54	14.80

[a] Results expressed as μg equiv. in 24-h period following dose application.

Table 5
Selected organ concentrations of radioactivity 24 h after a single dose, 7 or 14 daily doses of musk xylene or musk ketone expressed as μg equivalents compound/g tissue (average of two animals each)

Tissue	Musk xylene			Musk ketone		
	1 dose	7 doses	14 doses	1 dose	7 doses	14 doses
Kidney	0.039	0.028	0.043	0.052	0.097	0.19
Liver	0.083	0.083	0.12	0.17	0.24	0.53
Thyroid	0.057	0.11	0.085	0.064	0.15	0.18
Fat	0.19	0.18	0.22	0.056	0.10	0.15
Whole blood	0.012	0.0068	0.116	0.094	0.078	0.24

spectrum indicated that this metabolite was also the hydroxymethyl derivative. This was confirmed by ^{1}H-NMR, which showed the lack of a signal attributed to one methyl group but a new signal at lower field assigned to an oxidised methyl group.

Two aglycones of biliary musk ketone metabolites were isolated but no interpretable mass spectra were obtained that allowed structural assignments.

4. Discussion

These studies have shown that after a single 6-h occluded exposure, all three musks are extensively absorbed through rat skin in the order musk ambrette > musk ketone > musk xylene. While a similar order might be expected in humans, the amount absorbed under normal exposure conditions to a fragrance ingredient would be expected to be considerably less since absorption is typically significantly higher in rats and the occlusion used in these studies would enhance penetration.

Most of the absorption occurred during the 6-h exposure period but not all the material could be removed from the skin by washing and absorption of at least some of this residual material continued during the experimental period. At 8 h 8–10% of the applied dose remained in the skin, which declined to 2–3% at 120 h. Absorption appeared to be complete by about 48 h and thereafter the residual material in the skin was either absorbed so slowly that its decline profile could not be defined during the timescale of the experiment or it was bound to the skin matrix and only depleted by external desquamation.

Most of the absorbed material was excreted in faeces (ratio faeces:urine about 3:1) indicating the possibility of biliary excretion. Experiments in bile duct cannulated rats confirmed this and the extensive excretion by this route accompanied by very low urinary excretion indicates substantial enterohepatic circulation.

The bioaccumulation after 14 days of repeated application was remarkably small. It appears, based on urinary and faecal excretion, that a steady state excretion pattern was achieved after 9–13 days for both materials (Table 4). There was no appreciable accumulation of musk xylene in tissues at the end of the 14 days. On the other hand, for musk ketone, the 14-day levels were 2.5–3.6 times higher than after only one dose. It appears that both materials reach a steady state in a relatively short period and continued accumulation over longer time periods is not expected. This is supported by the fact that the reports in human fat samples show no correlation with age even over a range of a 3-year-old infant up to up a 100-year-old man (Müller et al., 1996).

The major biliary metabolite for musk ambrette resulted from the addition of a single atom of oxygen atom followed by conjugation and excretion as the glucuronide. It is most likely that this oxidation would occur on the methyl group or in the t-butyl group. The loss of a fragment corresponding to a t-butyl in the electron impact spectrum provided evidence that the metabolite is a hydroxymethyl analogue of musk ambrette although ring oxidation cannot be ruled out.

Similarly, for musk xylene, the principle biliary metabolite was the result of addition of a single

oxygen, followed by excretion as the glucuronide. Here, a combination of mass spectrometry and NMR allowed the assignment of the structure as the benzyl alcohol formed by hydroxylation of the methyl group.

In both cases, it is evident that some reabsorption of the aglycones occurred accompanied by further metabolism and a relatively complex pattern of urinary metabolites.

The metabolism of musk ketone was more extensive lending to a more complex mixture of conjugated metabolites in bile. The metabolism and excretion of these compounds is very similar to that reported for 2,4-dinitrotoluene (Medinsky and Dent, 1983) and 2.6-dinitrotoluene (Long and Rickert, 1982). In both cases, a major metabolite was a glucuronide of the benzyl alcohol, which was extensively excreted in bile. On the other hand, the major rat urinary metabolites reported by Minegishi et al. (1991) after oral administration were the reduced amino derivatives. The findings here indicate that it is likely that these were formed in the gut after biliary excretion.

In conclusion, musk ambrette, musk ketone and musk xylene were all extensively absorbed in vivo by the rat when applied under occlusion. It can be expected that absorption by humans under normal exposure conditions to fragrance materials would be less. For musk xylene and musk ketone, it appears that, while there is some bioaccumulation after repeated daily dosing, it is not likely that this would continue over longer periods of time.

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