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Dr. Kellner
Dr. Eckert

Hoechst Aktiengesellschaft
Pharma Research
Radiochemistry

PHARMACOKINETIC STUDIES OF OCTOPIROX-¹⁴C AFTER DERMAL, ORAL
AND INTRAVENOUS ADMINISTRATION TO RATS

Study

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Pharmacokinetic studies of Octopirox-¹⁴C after dermal,
oral and intravenous administration to rats

Summary:

A dermal dose of approximately 2 mg/animal Octopirox-¹⁴C in a 1.3 % shampoo preparation was applied onto fur and back skin (area: 4 cm²) of rats and rubbed in for one minute. Subsequently the treated site was wiped with wet cotton wool pads, and by this procedure 43.1 ± 7.2 % of the dose administered was removed. During the 7 days of study, between 0.64 and 2.27 % ($\bar{x} \pm s = 1.40 \pm 0.82$ %, n = 4) of the administered dose was renally excreted, 0.84 - 5.76 % ($\bar{x} \pm s = 3.10 \pm 2.26$ %) was fecally excreted. On the last day of study less than 0.3 % of the administered dose was recovered in excretory products. This slight absorption process still measurable may have been due to a possible reservoir formation caused by wiping the treated site with a wet cotton wool pad.

After oral administration of 0.24 mg/kg Octopirox, maximum compound levels in blood of 0.006 - 0.014 ug/ml were measured between 3 and 8 hours after treatment. Half-lives around 42 minutes and 14 hours were estimated for the biphasic elimination from blood after intravenous treatment. Independent of the route of administration, more radioactivity was excreted in feces (56 - 79 %) than in urine (12 - 22 %). After intravenous injection the administered radioactivity was, uninfluenced by absorption, eliminated with half-lives of about 8 and 23 hours or 35 hours. Depending on the experimental group, absorption ranged around 68 ± 10 % or may be considered complete (93 ± 14 %). Seven days after treatment the residues were less than 1 ppb except in the liver of 2 rats. Specific cumulations were not observed.

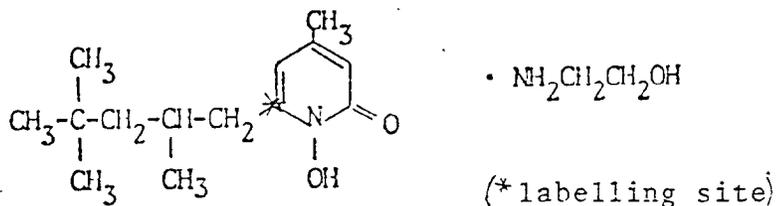
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1. Introduction

Studies on absorption after dermal application of the anti-dandruff agent Octopirox were to be performed in rats. The compound was also administered orally and intravenously in order to obtain data on the basic kinetic behaviour of the substance.

2. Material and methods

2.1 Radioactive labelled compound



Octopirox-(pyridone-6¹⁴C)-ethanolamine salt

Two Octopirox-¹⁴C batches with a specific radioactivity of 109 mCi/g = 40.33 x 10⁸ Bq/g (Batch No. 9027 I) and 94.9 mCi/g = 35.1 x 10⁸ Bq/g (Batch No. 9027 II) were employed. The compounds of either batch were radiochemically pure (> 98 %, cf. Figures 1a + 1b).

2.2 Dermal application

2.2.1 Preparation

The shampoo containing Octopirox-¹⁴C consisted of the following ingredients:

Part A	71.43 %	Genapol CRO fluid (28 %)
	3.00 %	Comperlan KD
	23.72 %	Water
Part B	1.50 %	Octopirox- ¹⁴ C
Part C	0.35 %	Citric acid (with 1 mol water of crystallisation)
	100.00 %	

The shampoo was prepared as follows: 1.5 g Octopirox-¹⁴C was dissolved in 98.15 g shampoo base (Part A) with stirring at room temperature (12 - 20 ml). Subsequently 350 mg citric acid ($\text{HO}\cdot\text{C}(\text{CH}_2\cdot\text{CO}_2\text{H})_2\text{CO}_2\text{H}\cdot\text{H}_2\text{O}$; mfr.: Riedel de Haën, No. 33114) was added within 5 minutes with stirring at room temperature; in this process the viscosity of the solution increased markedly. The pH value of the solution was about 7.0.

The content of active substance, which was determined radio-metrically, amounted to 13 mg Octopirox-¹⁴C per g shampoo.

2.2.2 Dose and administration

The amount of shampoo to be used was weighed onto a glass slide, was applied onto an approximately 2 x 2 cm-sized area of the back skin and was then rubbed in for 1 minute. The shampoo was applied and rubbed in with a finger protected by a rubber cap. Twenty-four hours prior to application the fur of the treated site had been clipped with a shearing device (Aesculap Favorita, mfr.: Aesculap, Tuttlingen, Fed. Rep. of Germany). This procedure is so gentle that the skin is not irritated. The shampoo was given 4 minutes to take effect, and then it was washed off from the treated site by means of cotton wool pads which had been moistened with water of body temperature. The rats received a plastic collar to keep them from licking the shampoo off the treated site and thus taking in the compound orally. In addition, the treated site was covered with a porous dressing, and for this procedure the rats were briefly anaesthetised (ether pro narcosi, mfr.: Hoechst AG).

The active substance in the shampoo which had remained on the glass slide and on the finger cap, in the cotton wool pad, in the washing solution and in the dressing, was determined by measuring the radioactivity.

The values measured in the above process are given in Table 1. A slightly larger weighed shampoo portion than the scheduled 115 mg/rat was used because of a possible loss in transferring the shampoo from glass slide to the rat. Measurement of the shampoo remainder revealed slighter losses, so that, with values ranging from 1.89 to 2.07 mg Octopirox-¹⁴C, the administered dose was between 27 and 38 % higher than the scheduled dose of 1.5 mg/animal.

2.3 Oral and intravenous administration

2.3.1 Preparation and dose

The scheduled dose was 0.2 mg/kg Octopirox-¹⁴C. For both routes of administration, Octopirox-¹⁴C was dissolved in polyethylene glycol 400. The active substance concentrations of the individual batches ranged between 0.033 and 0.043 µg/ml.

The compound was given intragastrically by means of a stomach tube or was intravenously administered as a single dose into a tail vein.

2.4 Experimental animals and animal maintenance

Healthy male SPF Wistar rats (breeder: Ivanovas, Kißlegg/Allgäu, Fed. Rep. of German) served as experimental animals. Data on the animals treated orally and intravenously and the weights of these animals at the beginning of the study are given in Table 2.

The kinetic studies after oral and intravenous treatment were carried out in intraindividual comparison. The rats were separated into 2 groups, of which one was used for the compound level in blood measurements, while the other one was employed for excretion studies. All rats received Octopirox-¹⁴C orally, and 14 days later they received the compound

intravenously. The study duration after either route of administration was 7 days. Between oral and intravenous administration there was a 7-day period without any treatment. At the end of the study, i.e. 7 days after intravenous injection, radioactive residues were measured in various organs and tissues of one experimental group (R₄₃ - 45). For this examination, the rats were stunned and then killed by exsanguination. The animals were dissected immediately after killing.

Throughout the study the rats were kept individually in metabolism cages with a device for separate urine and feces collection.

Blood samples were withdrawn from the retrobulbar venous plexus.

The rats received the standard feed Altromin^R (mfr.: Altrogge, Lage/Lippe, Fed. Rep. of Germany) which had been ground for this study. Feed and drinking water (municipal supply mains) were provided ad libitum throughout the study. The studies were conducted in air-conditioned metabolism rooms with a relative humidity of 45 - 55 % and a temperature of 21 ± 1°C.

2.5 Radioactivity measurements

The radioactivity in blood was measured after dissolving 0.1 ml blood in 1.5 ml digestin/water (1:4) and decolouring with 0.2 ml perhydrol after adding an emulsifying scintillator. In urine, the radioactivity was determined by direct addition of scintillator. The feces were homogenised, dried at room temperature and combusted in a Tri-Carb sample oxidiser (model 306, mfr.: Packard Instrument Company), and the ¹⁴CO₂ developing in this process was absorbed with Carbo-Sorb^R. The skin was dissolved in digestin (mfr.: Merck, Darmstadt, Fed. Rep. of Germany), and the remainder

of the body was dissolved in KOH.

Depending on size and quantity, the organs and tissues were cut or homogenised with twice the amount of water, and an aliquot of this homogenate was dissolved in digestin at 60 - 70°C.

All radioactivity measurements were performed by means of liquid scintillation, using an external standard device which permitted a determination of counting efficiency by means of the channel comparison method. In the studies, blank values were measured and subtracted from the measured values. These blank values were measured in biological material (blood, urine, feces) which had been obtained from the rats prior to Octopirox-¹⁴C treatment or from untreated animals (organs and tissues). Depending on the amount of material available, up to 3 parallel samples were examined.

A mixture suited for colloid formation and consisting of xylol, a polyethoxy ethanol, ethanol, 1.1% PPO and 0.1 % dimethyl POPOP served as scintillation liquid. This scintillator is comparable to Instagel (mfr.: Packard Instrument Company, U.S.A.) or Unisolve (mfr.: Kochlight, G.B.). The ratio of aqueous samples to scintillation liquid was always chosen to the effect that clear, homogenous measuring samples were available.

2.6 Whole-animal autoradiography

Immediately after killing with gaseous nitrogen, the rats were placed into a metal form, embedded in a 10 % Tylose solution (Tylose^R, mfr.: Hoechst AG) and by immersion into liquid nitrogen with the embedding medium frozen to a solid block. The rats thus prepared were stored in a deep-freezer at -20°C. The 25_{um}-thick frozen sections, cut with a cryomicrotome (type 450 MP, mfr.: PMV, Stockholm) at -20°C.

were lyophilised, placed on a highly sensitive x-ray film (Ultrofilm, LKB) and developed after a 57-day exposure period.

2.7 Notes on mathematical evaluation

The half-lives were determined by means of graphical analysis (feathering) and theory of adjustment. The main criterion for determining the limits of validity of individual phases was the coefficient of determination, r^2 . The concentrations given in μg represent the total of original substance and all radioactive labelled metabolites. The metabolism was not taken into consideration.

3. Results

3.1 Dermal application

By wiping the treated site with water-soaked pads, between 35 and 51 % ($\bar{x} \pm s = 43.1 \pm 7.2$ %) of the radioactivity administered was removed (Table 1). In the dressing used for covering the treated site, between 1.3 and 11.3 % ($\bar{x} \pm s = 6.1 \pm 5.1$ %) of the radioactive dose was recovered at the end of the study. The total Octopirox- ^{14}C quantity recovered from the skin amounted to 49.2 ± 3.2 %.

In 7 days of study, between 0.64 and 2.27 % ($\bar{x} \pm s = 1.40 \pm 0.82$ %) of the administered dose was renally excreted, and between 0.84 and 5.76 % ($\bar{x} \pm s = 3.10 \pm 2.26$ %) was fecally excreted (Tables 1, 3).

There was obviously a rapid onset of dermal absorption because the largest amounts of renally excreted radioactivity were measured in the first two urine fractions (0 - 3 and 3 - 7 hours after treatment), taking the varying long collection intervals into consideration. After the first day of study almost 1.4 %, i.e. about 30 % of the radioactivity

recovered in urine and feces in 7 days, had been excreted.

Radioactivity excretion was not fully completed at the end of the study, as almost 0.3 % of the radioactive dose was renally and fecally excreted on the last day of study.

From the gradient of the excretion curves, half-lives of 50 - 173 hours ($\bar{x} \pm s = 92 \pm 55$ h) in urine and, from the second day of the study onward, of 77 - 173 hours ($\bar{x} \pm s = 122 \pm 43$ h) in feces were calculated (Figures 2, 3). These half-lives were not the half-lives of active substance elimination from the body. The elimination half-lives were shorter, as studies after intravenous injection revealed (cf. discussion on page 14).

3.2 Intravenous and oral administration

3.2.1 Compound levels in blood

The concentrations measured in blood (μg equivalents of Octopirox) are given in Table 4 and illustrated in Figure 4.

After oral administration of 0.24 mg/kg Octopirox- ^{14}C , compound levels in blood were soon measurable (0.004 ± 0.001 $\mu\text{g}/\text{ml}$ at 0.25 h after treatment). They slowly increased and reached values between 0.006 and 0.014 $\mu\text{g}/\text{ml}$ 6 - 8 hours after treatment. The course of the curve indicates that maxima might have been reached later than 8 hours after treatment, but most likely they were not higher than the values of 0.009 ± 0.004 $\mu\text{g}/\text{ml}$ measured 8 hours after treatment.

After intravenous injection of 0.21 mg/kg Octopirox- ^{14}C to the same animals, the blood concentrations 5 minutes after treatment were only 4.6 ± 0.95 % ($n = 3$) of those which would have been expected assuming compound distribution only in the blood (5.5 % of body weight). The elimination curve is obviously the result of the overlapping of different processes (Figure 4).

Table 5: Kinetic parameters of compound levels in blood after oral administration of 0.24 mg/kg Octopirox-¹⁴C

	R ₄₀	R ₄₁	R ₄₂	$\bar{x} \pm s$
t _{max} (h p.appl.)	8	8	3	6.33 \pm 2.9
c _{max} (µg/ml)	0.006	0.014	0.008	0.009 \pm 0.004
AUC _{24 h} (µg/ml·h)	0.1074	0.1746	0.1216	0.1345 \pm 0.0354

Table 6: Kinetic parameters of compound levels in blood after intravenous injection of 0.21 mg/kg Octopirox-¹⁴C

R ₄₀₊₄₁ 1)	Y _{B₀α} (µg/ml)	Y _{B₀β} (µg/ml)	t _{1/2} (h)	r ²	Range (h after treatment)
α-Phase	0.106		0.69	0.89	0.25 - 3
β-Phase		0.0063	14.4	0.98	6 - 24
AUC _{24 h}	R ₄₀	F ₄₁	R ₄₂		
µg/ml·h	0.2125	0.1611	1)		

1) R₄₂ died 2 hours after treatment

The curve of compound levels in blood may best be described by two exponential functions:

$$Y_B(t) = Y_{B_{0\alpha}} \times e^{-\alpha t} + Y_{B_{0\beta}} \times e^{-\beta t}$$

In this function,

$Y_B(t)$ = total concentration in blood at time t ,

$Y_{B_{0\alpha}}$ and $Y_{B_{0\beta}}$ = fictive initial concentration in blood for the α and β -phase,

and α and β = elimination constants.

Based on these functions, the kinetic characteristics with half-lives of 41.5 minutes and 14.4 hours, given in Table 6, were obtained. The values of only 2 rats were evaluated because rat No. 42 had died shortly after intravenous injection (too rapid injection?).

3.2.2 Excretion

The results are given in Tables 7 and 8; Table 9 gives a survey on excretion recovery.

The rats of both groups excreted radioactivity more with feces (56 - 60 %, R_{43-45} ; 73-79 %, R_{50-52}) than with urine, independent of the route of administration. The amount of radioactivity recovered in urine after oral treatment was less than that recovered after intravenous injection. It amounted to 12 % of the dose administered in one group⁺ and to about 20 % in the other group⁺ (Table 9). The absorption calculated from the ratio of radioactivity renally excreted after oral and intravenous treatment was 68 ± 10 % (R_{50-52}) in one group and 93 ± 14 % in the other group ($R_{43 - 45}$).

⁺including cage washings

The renal excretion was biphasic with half-lives between 7 and 9 hours and 23 and 36 hours (Table 10, Figures 5, 6). These values do not indicate differences within the range of variation which result from the route of administration.

The individual variations in fecal excretion were considerable in some cases. For kinetic evaluation, the mean values of one group were therefore used in some cases. The half-lives ranged in the same order as in renal excretion (Table 10, Figure 7).

Within the framework of excretion studies it was also examined whether radioactivity was eliminated in breath. For this examination, the respiratory air of 2 rats which were kept in a special metabolism cage, was sucked off through an exhalometer (type FHT 50 B, mfr.: Frieseke & Hoepfner, Erlangen, Fed. Rep. of Germany) and its radioactivity content was determined. At a limit of detection of 41 % of the dose administered, no radioactivity was demonstrable.

3.2.3 Examination of distribution and residues

The distribution of radioactivity was examined autoradiographically in short intervals after treatment.

After intravenous injection of Octopirox-¹⁴C, the radioactivity was distributed in the entire organism and was concentrated mainly in the excretory organs liver and kidneys 5 minutes after injection (Figure 8). Remarkable concentrations were also measured in the lungs. One hour after intravenous injection, the periphery was virtually free from radioactivity, and at this time high radioactivity concentrations were measured in the small and large intestine (Figure 9). Liver and kidneys showed almost the same concentrations, but they were markedly lower than those

measured 5 minutes after injection. One day after intravenous injection, only the intestinal contents showed low radioactivity levels, radioactivity was no longer autoradiographically demonstrable in the kidneys, and only traces of radioactivity were measurable in the liver (Figure 10).

Despite a principally similar distribution pattern as after intravenous injection, after oral treatment the radioactivity in liver, kidneys and skeletal muscles was markedly lower, which might be due to incomplete absorption (Figures 11 - 13).

The high radioactivity concentrations measured in the intestine after intravenous injection indicate, in connection with the concentration in the liver, a predominantly biliary elimination.

Specific cumulations in organs and tissues persisting for a longer period were not observed in autoradiography.

Seven days after intravenous injection of Octopirox-¹⁴C, the residues in organs and tissues given in Table 11 were determined by means of liquid scintillation. The animals (R₄₃₋₄₅) had already received a single oral Octopirox-¹⁴C dose 21 days prior to this date of examination.

With the exception of the liver values of 2 rats which showed concentrations of 1 ng/g (1 ppb), the values of all other organs and tissues examined were below the limit of detection of 1 ng/g.

4. Discussion

After topical application, the mean absorption rate determined in 7 days of this study was 4.5 %, with individual variations ranging between 1.5 and ~~8~~%. The slight absorption (0.3 % on day 7) still measurable at the end of the study was obviously attributable to a reservoir in or on the skin, the cause of which might have been the insufficient removal of the active substance from the skin, as only between one third and half of the applied active substance was removed with the water-soaked cotton wool pads (Table 1). In another study conducted according to the same design, similar values (37 - 42 %) were measured (Table 12). Skin and hair of the treated site contained between 36 and 43 % of the administered dose. At the end of the study (8 hours after treatment), approximately 1.9 % of the dose was measured in the body, and slightly less than 0.1 % had been excreted in urine and feces, so that an absorption of almost 2 % was calculated for this period (Table 12). These values are comparable to those measured in the first study.

It may be assumed that the amount of shampoo washed off would have been larger if a larger volume of rinsing water, as is normally the case in practice, had been used, which would have further reduced transdermal substance transport.

The long half-lives at 100 hours after dermal application do not describe the elimination of active substance (and/or its radioactive labelled metabolites) from the organism. The slow substance transfer from the skin to the systemic circulation is to be considered the step determining the elimination rate. Therefore the elimination, which was not influenced by absorption, was considerably faster, as the determination of pharmacokinetic parameters after intravenous injection showed. Half-lives around 8 and 23 hours or 35 hours were measured. The values measured after oral treatment were similar.

The very low concentrations measured at the end of the study in organs and tissues examined and which, with the exception of liver values (1 ppb) of 2 rats, all were lower than 1 ppb, indicate complete elimination. Specific accumulations persisting for a longer period after oral and intravenous administration were not observed in autoradiographic studies either.

The following persons were also engaged in this study:

Synthesis: Dr Herok, Department of Radiochemistry

Tests for purity: Dr Löttsch, Department of Radiochemistry

Department of Radiochemistry

of

HOECHST AG

Signed:

Dr Kellner

Dr Eckert

Table 1: Recovery after dermal application of 1.3 % Octopirox-¹⁴C shampoo

	R ₄₆	R ₄₇	R ₄₈	R ₄₉
Octopirox- ¹⁴ C available for this study (mg)	2.148	2.202	2.249	2.170
Amount applied ¹⁾ (mg)	1.893	2.068	2.010	2.010
Amount wiped off				
mg	0.742	0.725	0.952	1.020
%	39.20	35.06	47.36	50.75
Remainder in dressing (mg)	0.214	0.200	0.0446	0.0268
%	11.3	9.67	2.22	1.33
Excretion (%)				
Urine	2.27	1.93	0.64	0.75
Feces	5.76	4.13	0.84	1.64
Balance	58.53	50.79	51.06	54.47

1) corresponds to dose

Table 2: Animal Nos. and Weights

	dermal	Route oral	intravenous
Blood level	(g)	(g)	(g)
R ₄₀		180	210
R ₄₁		180	220
R ₄₂		180	200
Excretion	(g)	(g)	(g)
R ₄₃		180	230
R ₄₄		180	220
R ₄₅		180	230
R ₅₀		200	250
R ₅₁		190	250
R ₅₂		250	250
R ₄₆	250		
R ₄₇	300		
R ₄₈	350		
R ₄₉	250		
R ₆₁	300		
R ₆₂	300		
R ₆₃	270		
Autoradiography		(g)	(g)
R ₅₃			250
R ₅₄			250
R ₅₅			250
R ₅₆		250	
R ₅₇		250	
R ₅₈		250	

Table 3: Excretion in urine and feces after dermal application of 1.3 % Octopirox-¹⁴C-shampoo to rats

Time	Dose administered (mg Octopirox- ¹⁴ C)				
	1.893	2.068	2.010	2.010	1.995
	U R I N E				
	R ₄₆	R ₄₇	R ₄₈	R ₄₉	\bar{x}
	% of radioactivity administered				
0-3 h	0.11	0.098	0.034	0.009	0.065
3-7	0.087	0.11	0.041	0.032	0.068
7-24	0.54	0.40	0.091	0.12	0.29
24-48	0.59	0.32	0.10	0.10	0.28
48-72	0.39	0.24	0.10	0.11	0.21
72-96	0.21	0.28	0.084	0.10	0.17
96-120	0.12	0.19	0.057	0.09	0.11
120-144	0.11	0.14	0.069	0.11	0.11
144-168	0.12	0.16	0.067	0.08	0.11
0-168 h	2.27	1.93	0.64	0.75	1.40

Time	F E C E S				
	R ₄₆	R ₄₇	R ₄₈	R ₄₉	\bar{x}
	% of radioactivity administered				
0-24 h	2.02	1.04	0.35	0.38	0.95
24-48	1.71	0.91	0.30	0.50	0.86
48-72	0.71	0.41	0.049	0.18	0.34
72-96	0.39	0.84	0.049	0.17	0.36
96-120	0.37	0.23	0.033	0.16	0.21
120-144	0.27	0.38	0.033	0.13	0.20
144-168	0.29	0.27	0.033	0.12	0.18
0-168 h	5.76	4.13	0.84	1.64	3.10

Table 4: Compound levels in blood after intravenous and oral administration of Octopirox-¹⁴C to rats

Time after treatment	Oral					Intravenous			
	Concentration: (µg/ml)								
	0.24 mg/kg p.o.					0.21 mg/kg iv.			
	R ₄₀	R ₄₁	R ₄₂	\bar{x}	s	R ₄₀	R ₄₁	\bar{x} _{P40-41}	R ₄₂ ¹⁾
0.083 h						0.176	0.138	0.157	0.209
0.25	0.005	0.003	0.005	0.004	0.001	0.121	0.095	0.108	0.211
0.5	0.005	0.003	0.005	0.004	0.001				
0.75						0.042	0.035	0.039	0.128
1	0.005	0.003	0.006	0.005	0.002	0.031	0.028	0.030	0.115
3	0.004	0.005	0.008	0.006	0.002	0.014	0.009	0.012	
6	0.004	0.009	0.008	0.007	0.003	0.005	0.004	0.005	
8	0.006	0.014	0.007	0.009	0.004	0.004	0.003	0.004	
24	0.003	0.001	0.001	0.002	<0.001	0.002	0.001	0.002	
32	0.002	0.001	0.001	0.001	<0.001	0.002	<0.001	0.002	
48	0.001	0.001	<0.001	0.001		<0.001	<0.001	<0.001	
72	0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
96	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
120	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
144	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
168	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
168.08	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	

¹⁾The rat died 2 hours after treatment (cf. report)

Table 7: Excretion in urine and feces after oral (0.24 mg/kg) and intravenous (0.22 mg/kg administration of Octopirox-¹⁴C to rats

	Oral					Intravenous					s	
	Time after treatment	R ₄₃	R ₄₄	R ₄₅	\bar{x}	Time after treatment	R ₄₃	R ₄₄	R ₄₅	\bar{x}		
	% of radioactivity administered											
Urine	0-4 h	1.90	1.12	1.36	1.46		0-4 h	6.16	6.13	8.55	6.95	
	4-8	2.94	1.92	1.94	2.27		4-8	1.05	1.88	2.00	1.64	
	8-24	8.03	8.18	8.94	8.38		8-24	3.95	6.70	8.28	6.51	
	0-1 d	12.87	11.22	12.24	12.11		0-1 d	11.16	14.71	18.83	14.90	
	1-2	2.39	3.69	3.38	3.15		1-2	2.78	2.96	4.27	3.34	
	2-3	0.87	3.09	1.50	1.82		2-3	1.14	1.24	1.52	1.30	
	3-4	0.39	0.65	0.68	0.57		3-4	1.10	0.58	0.81	0.83	
	4-5	0.19	0.54	0.49	0.40		4-5	1.30	0.33	0.34	0.66	
	5-6	0.13	0.75	0.38	0.42		5-6	0.54	0.18	0.18	0.30	
	6-7	0.07	0.33	0.25	0.22		6-7	0.28	0.14	0.14	0.19	
	0-7 d	16.91	20.27	18.92	18.70	1.69	0-7 d	18.30	20.14	26.09	21.51	4.07
Washing	1. d	0.48	0.79	1.31	0.86		1. d	0.41	0.33	0.21	0.32	
	2. d	0.33	0.73	0.51	0.52		3. d	0.12	0.14	0.16	0.14	
	7. d	0.04	0.23	0.18	0.15		7. d	0.10	0.08	0.10	0.093	
	0-7 d	0.85	1.75	2.00	1.53		0-7 d	0.63	0.55	0.47	0.55	
Feces	0-8 h	28.60	4.63	16.73	16.65		0-1 d	33.28	30.19	46.33	36.60	
	8-24 h	20.16	22.09	30.00	24.08		0-2	8.54	7.48	14.21	10.08	
	1-2 d	5.48	3.23	4.34	4.35		2-3	2.49	2.27	2.28	2.35	
	2-3	0.86	1.13	-	0.66		3-4	5.71	2.12	0.91	2.91	
	3-4	10.20	15.12	3.37	9.56		4-5	4.93	0.56	0.43	1.97	
	4-5	6.61	0.38	0.83	2.61		5-6	4.23	0.29	0.51	1.61	
	5-6	0.13	0.25	0.71	0.56		6-7	1.09	0.25	0.23	0.52	
	6-7	0.07	0.21	4.06	1.46							
	0-7 d	72.11	47.07	60.01	59.74	12.52	0-7 d	60.27	43.10	64.09	56.04	11.37
	Recovery	89.87	69.09	80.96	79.97	10.43	Recovery	79.20	63.86	91.25	78.10	13.73

Table 8 : Excretion in urine and feces after oral (0.19 mg/kg) and intravenous (0.21 mg/kg administration of Octopirox-¹⁴C to rats

	Oral					Intravenous					
	Time after treatment	R ₅₀	R ₅₁	R ₅₂	\bar{x}	s	R ₅₀	R ₅₁	R ₅₂	\bar{x}	s
% of radioactivity administered											
Urine	0-4 h	1.14	1.77	2.51	1.81		2.92	4.29	4.67	3.96	
	4-8	1.67	1.01	1.35	1.34		0.13	2.94	1.71	1.60	
	8-24	5.38	4.65	5.39	5.14		7.23	6.44	7.48	7.05	
	1-2 d	1.51	0.72	1.54	1.26		3.34	1.94	2.21	2.50	
	2-3	0.54	0.25	0.44	0.41		1.20	0.50	0.63	0.78	
	3-4	0.29	0.09	0.12	0.17		0.41	0.15	0.29	0.28	
	4-5	0.13	0.15	0.063	0.12		0.21	0.10	0.11	0.14	
	5-6	0.11	0.04	0.032	0.062		0.13	0.07	0.07	0.09	
	6-7	0.11	<0.01	0.051	0.054		0.03				
	0-7 d	10.88	8.68	11.50	10.36	1.48	15.58	16.42	17.23	16.41	0.83
Washing	1. d	0.76	0.85	1.27	0.96		0.46	0.59	0.23	0.43	
	2. d	0.37	0.12	0.17	0.22		0.22	0.14	0.06	0.14	
	7. d	0.085	0.06	0.047	0.63		0.03			0.01	
0-7 d	1.22	1.03	1.49	1.24		0.72	0.73	0.29	0.58		
Feces	0-1 d	44.36	85.39	58.31	62.68		65.97	68.71	69.87	68.18	
	1-2	3.68	1.30	3.09	2.89		9.97	7.26	5.87	7.70	
	2-3	1.27	0.46	11.05	4.26		1.44	2.31	1.49	1.75	
	3-4	7.61	0.22	0.18	2.67		0.36	0.85	0.47	0.56	
	4-5	0.19	0.083	0.054	0.11		0.18	0.39	0.26	0.28	
	5-6	0.073	0.029	0.040	0.047		0.15	0.16	0.13	0.15	
	6-7	0.079	<0.01	0.025	0.035		0.01	0.14	0.09	0.08	
	0-7 d	57.36	87.45	75.55	72.68	15.12	78.08	79.82	78.18	78.69	0.98
Recovery	69.36	97.18	86.34	84.28	14.02	94.38	96.97	95.70	95.68	1.30	

Table 9: Excretion in urine and feces after oral and intravenous administration of Octopirox-¹⁴C to rats

	^R ₄₃₋₄₅		^R ₅₀₋₅₂	
	Oral	Intravenous	Oral	Intravenous
	% of radioactivity administered			
Urine	18.70 ± 1.70	21.51 ± 4.07	10.56 ± 1.48	16.41 ± 0.83
Feces	59.73 ± 12.52	56.04 ± 11.37	72.68 ± 15.12	78.69 ± 0.98
Washing ¹⁾	1.53	0.55	1.24	0.58
Recovery	79.97 ± 10.42	78.10 ± 13.73	84.28 ± 14.02	95.68 ± 1.30
Dose (mg/kg)	0.24	0.22	0.19	0.21

1) Cage washing

Table 10: Half-lives of renal and fecal excretion of radioactivity after oral and intravenous administration of Octopirox-¹⁴C to rats

	R ₄₃₋₄₅		R ₅₀₋₅₂	
	Oral	Intravenous	Oral	Intravenous
U R I N E				
t _{1/2} (h) - Phase II	6.9 ± 0.6	8.1 ± 0.8	8.5 ± 2.6	7.8 ± 0.6
Range (h after adm.)	0 - 48	0 - 48	0 - 48	0 - 48
t _{1/2} (h) - Phase III	35.5 ± 7.3	34.6 ± 11.1	31.3 ± 8.9	22.5 ± 3.8
Range (h after adm.)	48 - 168	48 - 168	48 - 168	48 - 168
F E C E S				
t _{1/2} (h) - Phase II	~7.7	~9.9	~5.1	6.2 ± 1.0
Range (h after adm.)	4 - 48	0 - 48	0 - 48	0 - 48
t _{1/2} (h) - Phase III	1)	(~35)	1)	20.8 ± 4.7
Range (h after adm.)		(48-168)		48 - 168

1) Not determinable

Table 11: Distribution of radioactivity in organs 7 days after intravenous injection of 0.22 mg/kg Octopirox-¹⁴C to rats

	R ₄₃	R ₄₄	R ₄₅
	Concentration (µg/g)		
Spleen	<0.001	<0.001	<0.001
Adrenals	<0.001	(R ₄₃₋₄₅)	
Kidneys	<0.001	<0.001	<0.001
Gonads	<0.001	<0.001	<0.001
Liver	<0.001	0.001	0.001
Heart	<0.001	<0.001	<0.001
Lungs	<0.001	<0.001	<0.001
Skeletal muscles	<0.001	<0.001	<0.001
Retroperitoneal fat	<0.001	<0.001	<0.001
Brain	<0.001	<0.001	<0.001
Bone marrow	<0.001	(R ₄₃₋₄₅)	
Eyes	<0.001	<0.001	<0.001
Blood	<0.001	<0.001	<0.001
Subcutaneous fat	<0.001	<0.001	<0.001

Table 12: Recovery after dermal application of 1.24 % Octopirox-¹⁴C shampoo

	R ₆₁	R ₆₂	R ₆₃
Octopirox- ¹⁴ C available for this study (µg)	2422.56	2472.00	2422.56
Amount applied (µg)	2302.86	2360.09	2325.19
Amount wiped off (µg)	894.10	994.20	854.58
(%) ²⁾	38.8	42.1	36.8
Treated site (skin + hair) (µg)	825.30	910.80	1141.31
(%)	35.8	38.6	49.1
Excretion (%)			
Urine	0.0419	0.062	0.1553
Feces	0.0014	0.002	0.0073
Washing ³⁾	0.0019	0.0047	0.0043
Remainder of body	1.26	2.19	2.12
Recovery (%)	75.91	82.96	88.19

1) corresponds to dose administered

2) % of dose administered

3) cage washing

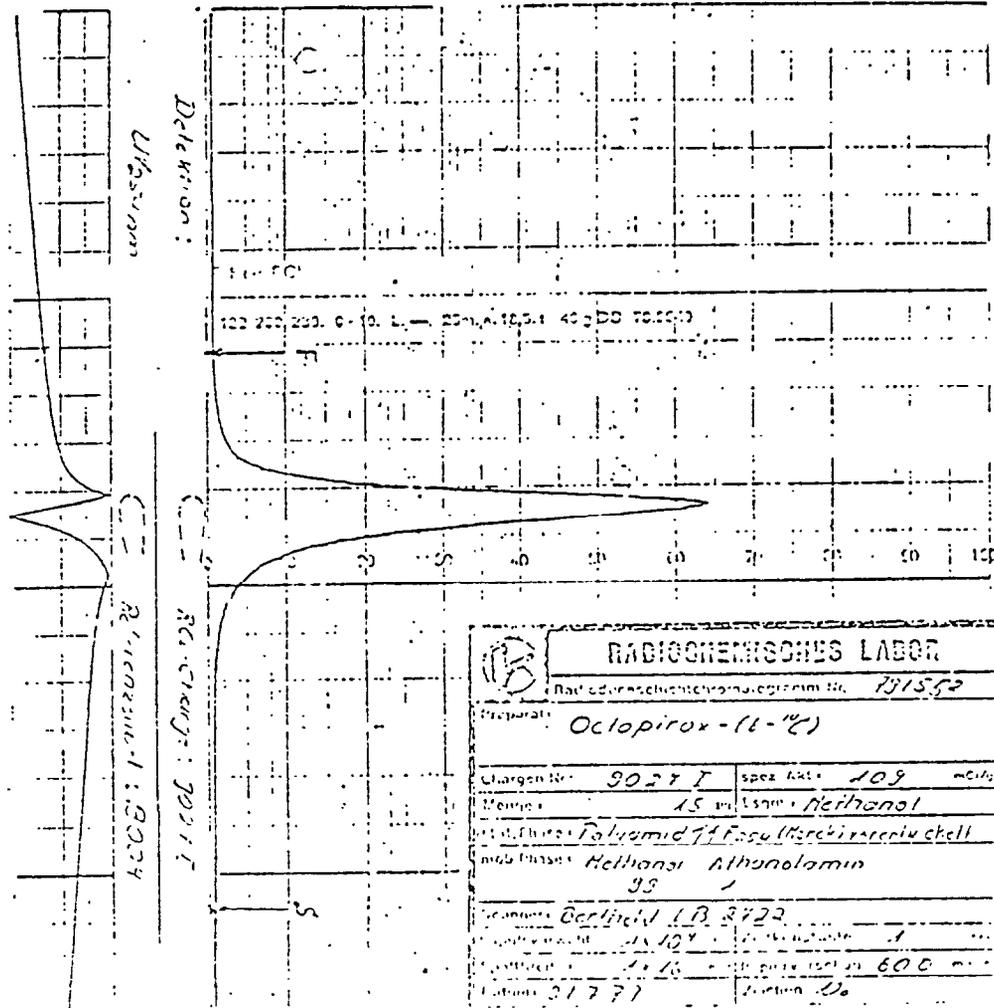


Figure 1a: Thin-layer radiochromatogram

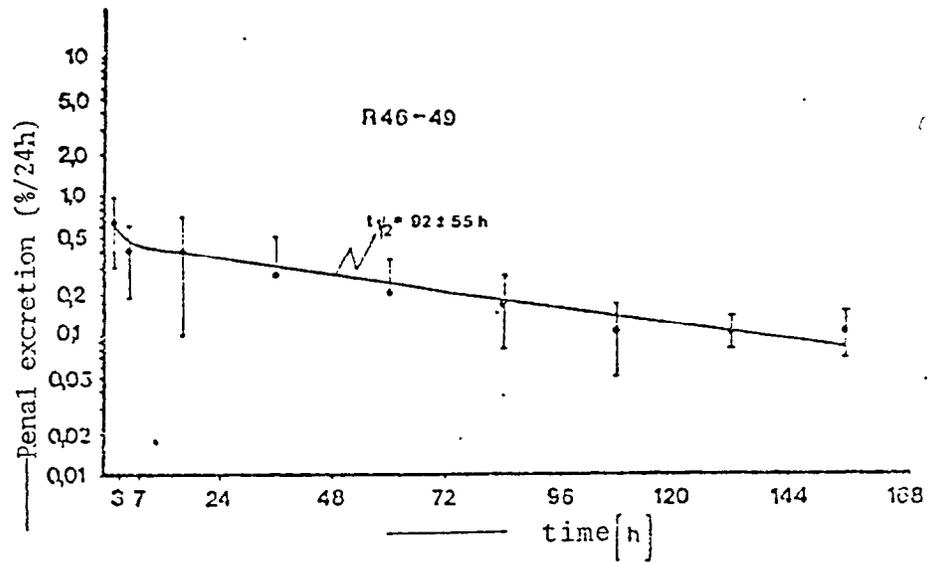


Figure 2: Renal excretion after dermal application of 1.3 % Octopirox-¹⁴C shampoo to rats

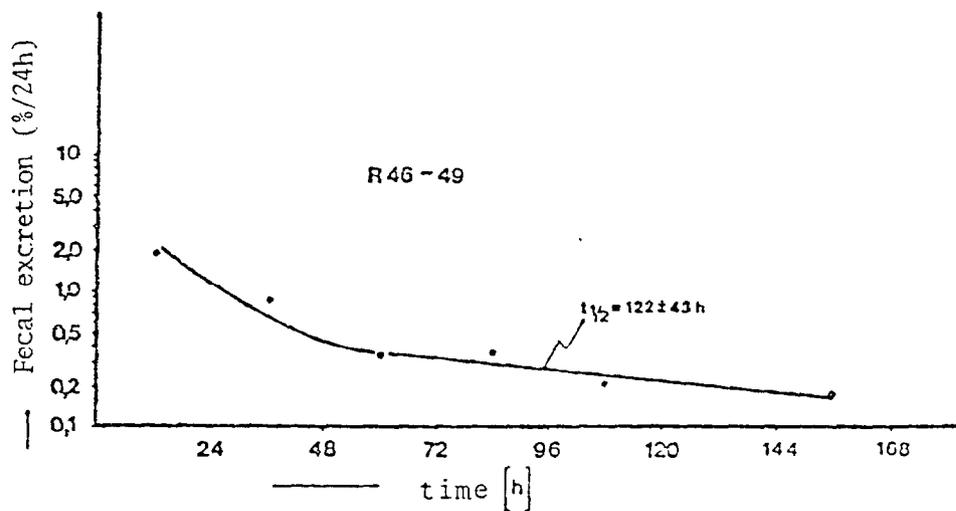


Figure 3: Fecal excretion after dermal application of 1.3 % Octopirox-¹⁴C shampoo to rats

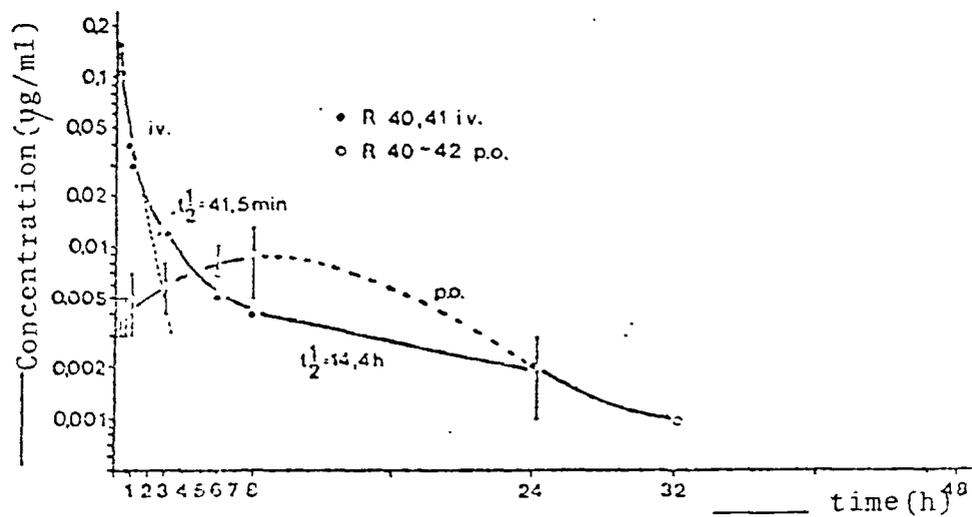


Figure 4: Compound levels in blood after intravenous (0.21 mg/kg) and oral (0.24 mg/kg) administration of Octopirox-¹⁴C to rats

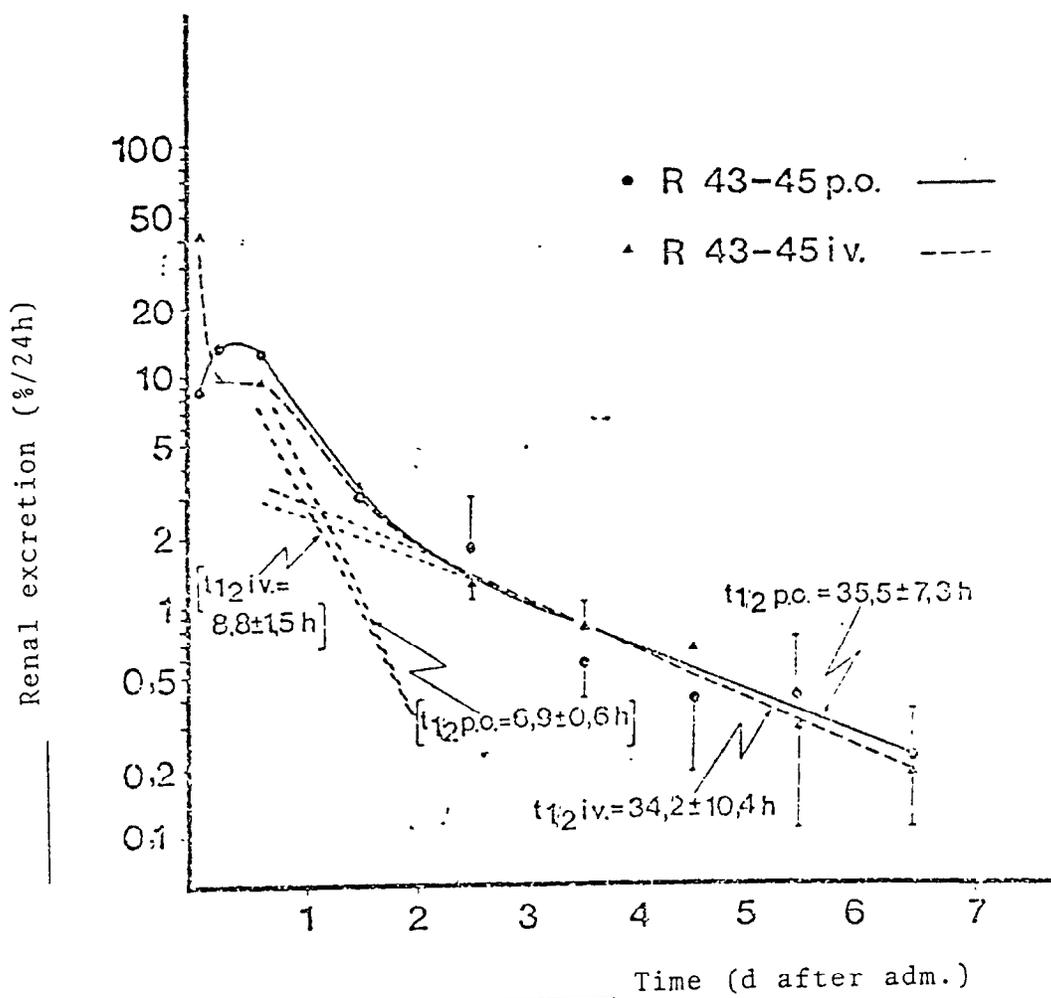


Figure 5: Renal excretion after intravenous (0.22 mg/kg) and oral (0.24 mg/kg) administration of Octopiros-¹⁴C to rats

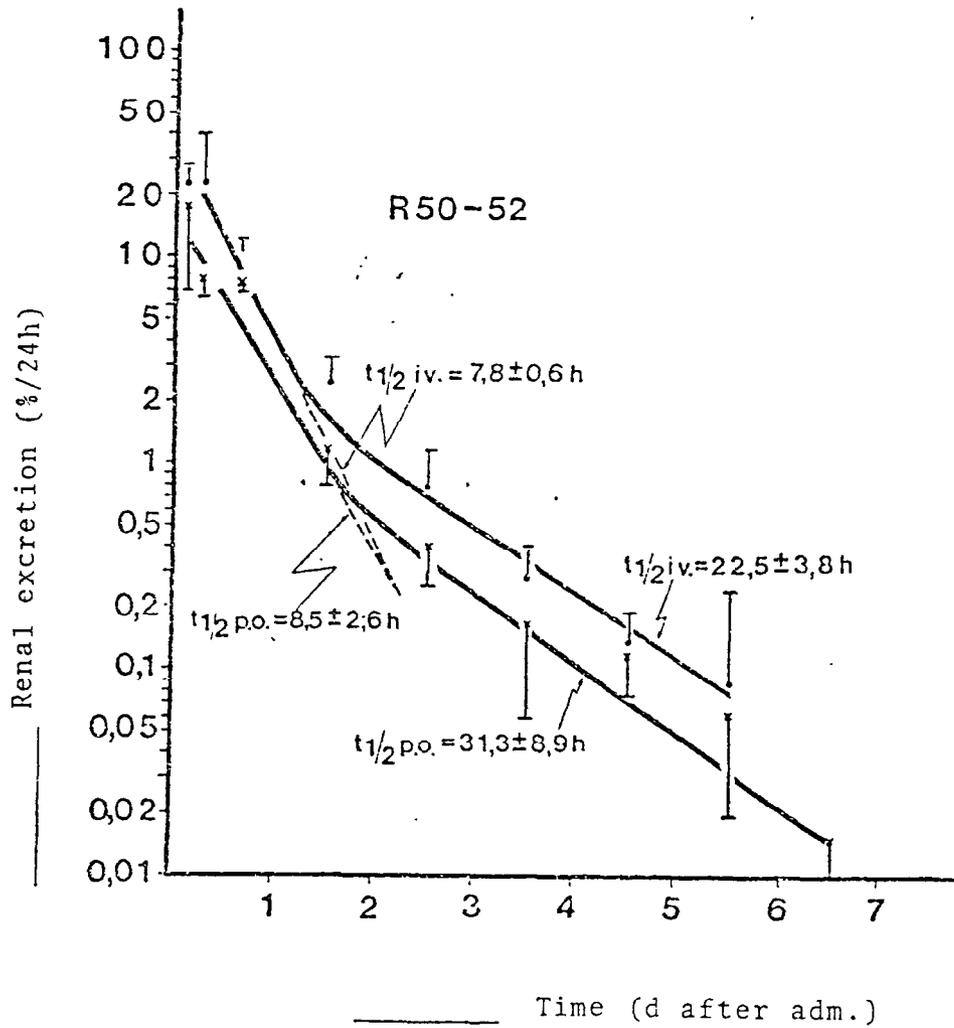


Figure 6: Renal excretion after intravenous (0.21 mg/kg) and oral (0.19 mg/kg) administration of Octopirox-¹⁴ to rats

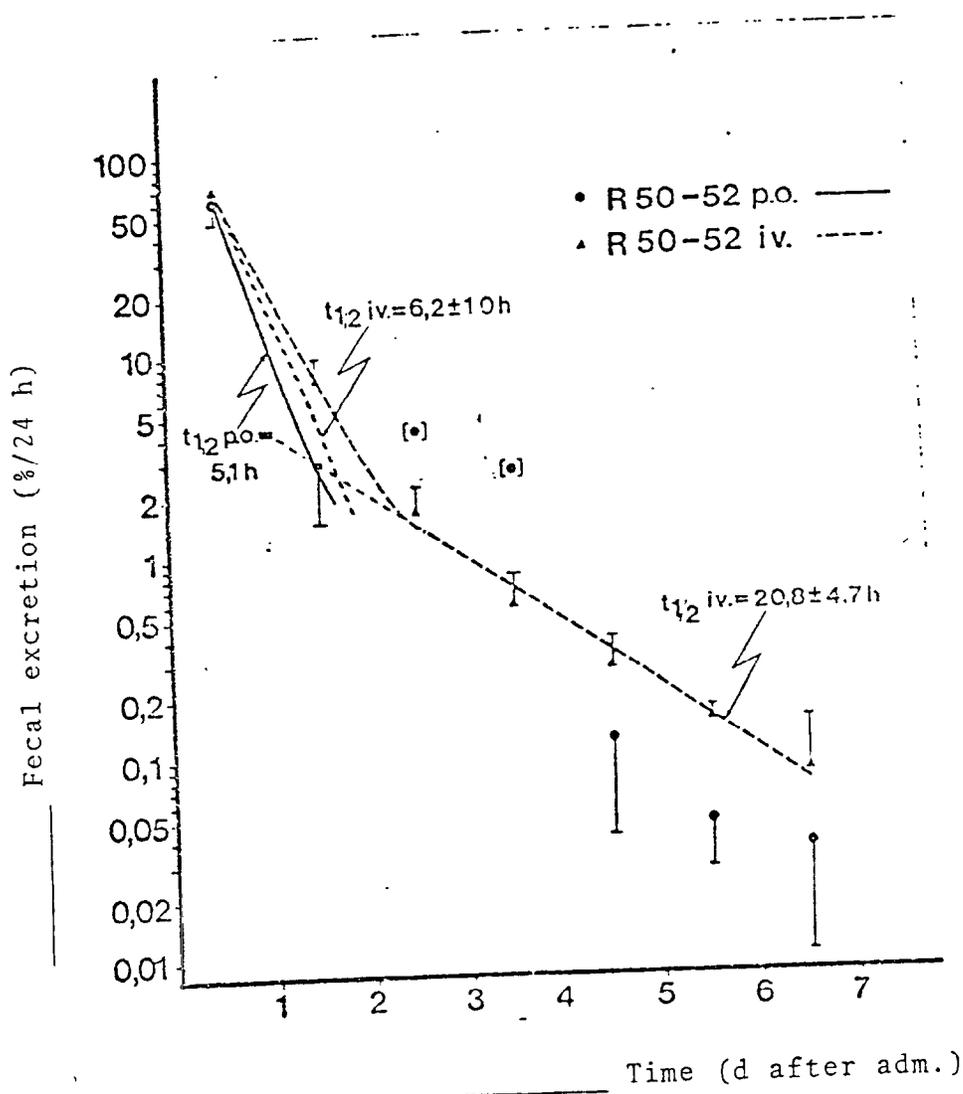


Figure 7: Fecal excretion after intravenous (0.21 mg/kg and oral (0.19 mg/kg) administration of Octopirox-¹⁴C to rats



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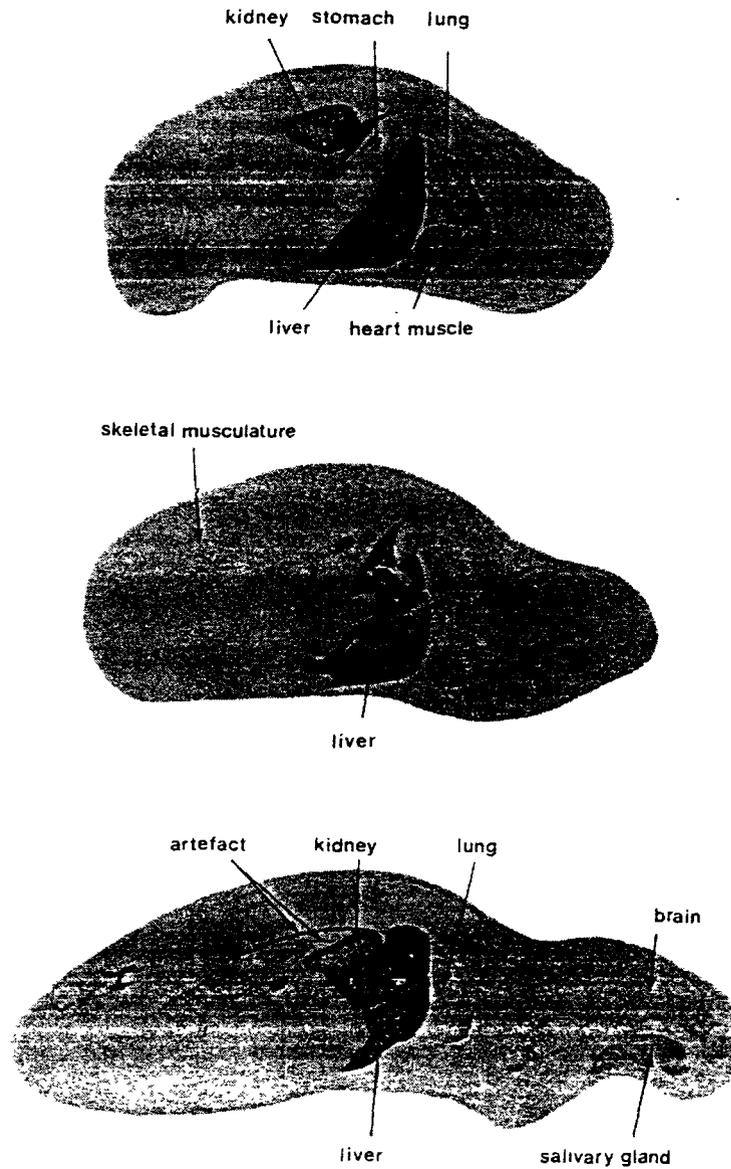


Fig. 8: Autoradiograms of sections of different body planes of a rat (R₅₃) 5 min after intravenous administration of 0.2 mg Octopirox-¹⁴C per kg body weight



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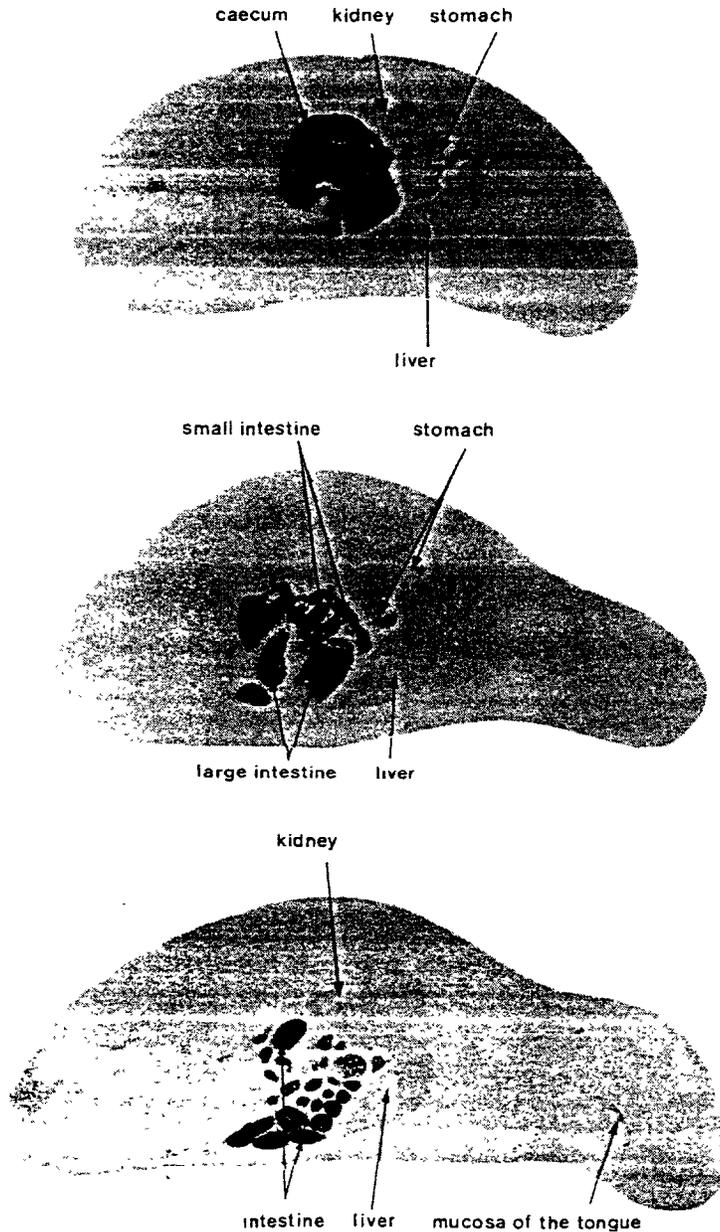


Fig. 9: Autoradiograms of sections of different body planes of a rat (R₅₄) 1 h after intravenous administration of 0.2 mg Octopirox-¹⁴C per kg body weight



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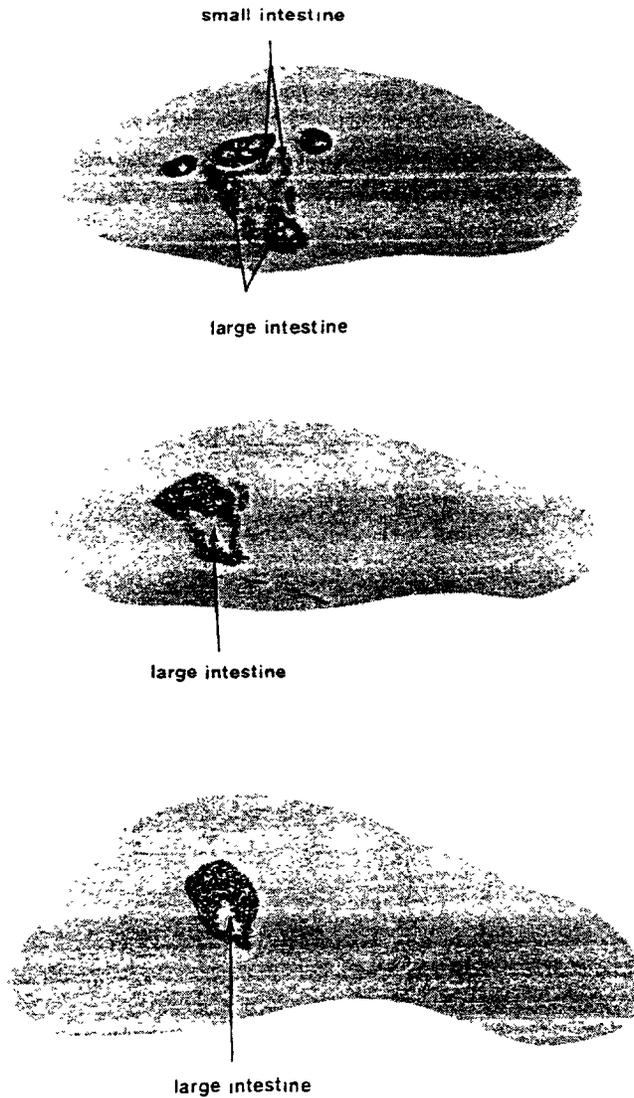


Fig. 10: Autoradiograms of sections of different body planes of a rat (R_{55}) 24 h after intravenous administration of 0.2 mg Octopirox- ^{14}C per kg body weight



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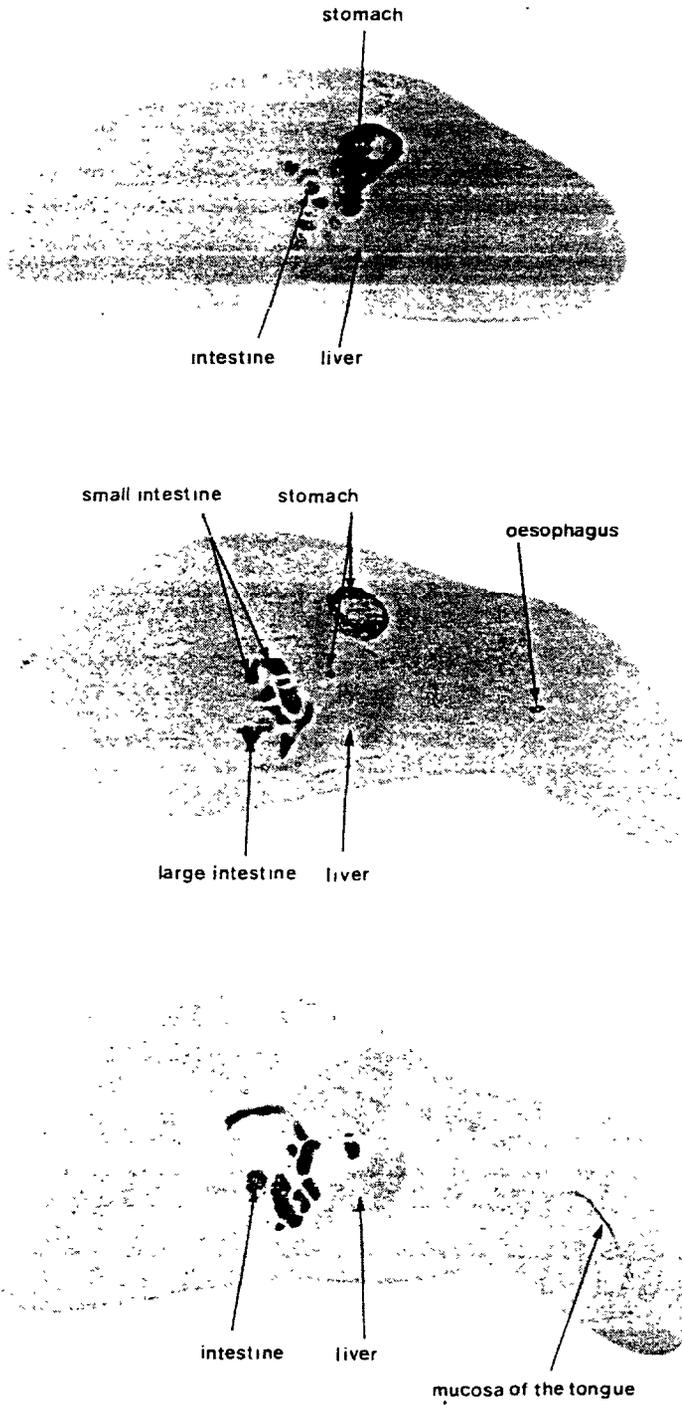


Fig. 11: Autoradiograms of sections of different body planes of a rat (R₅₆) 1 h after oral administration of 0.2 mg Octopirox- ^{14}C per kg body weight



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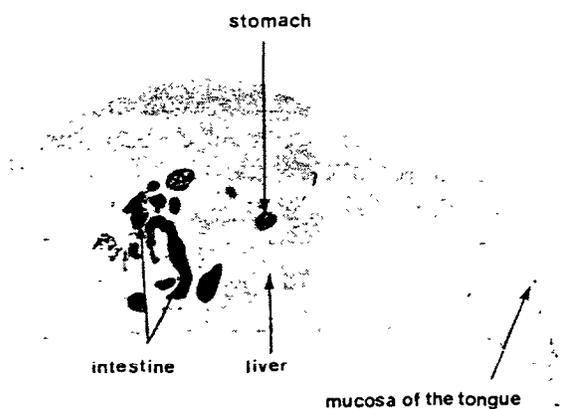
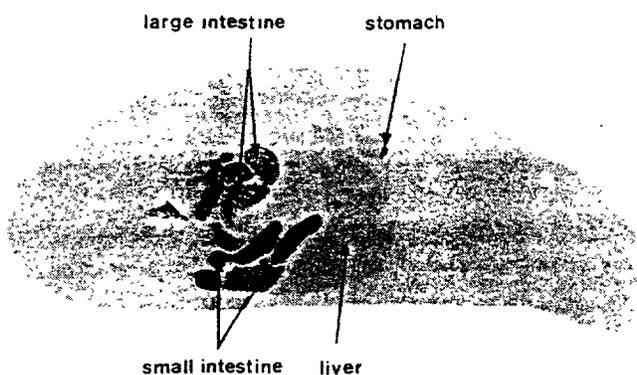
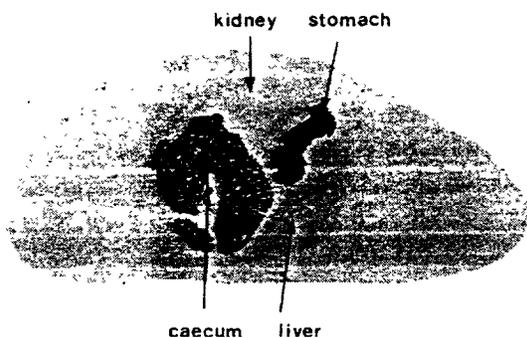


Fig. 12: Autoradiograms of sections of different body planes of a rat (R₅₇) 4 h after oral administration of 0.2 mg Octopirox-¹⁴C per kg body weight



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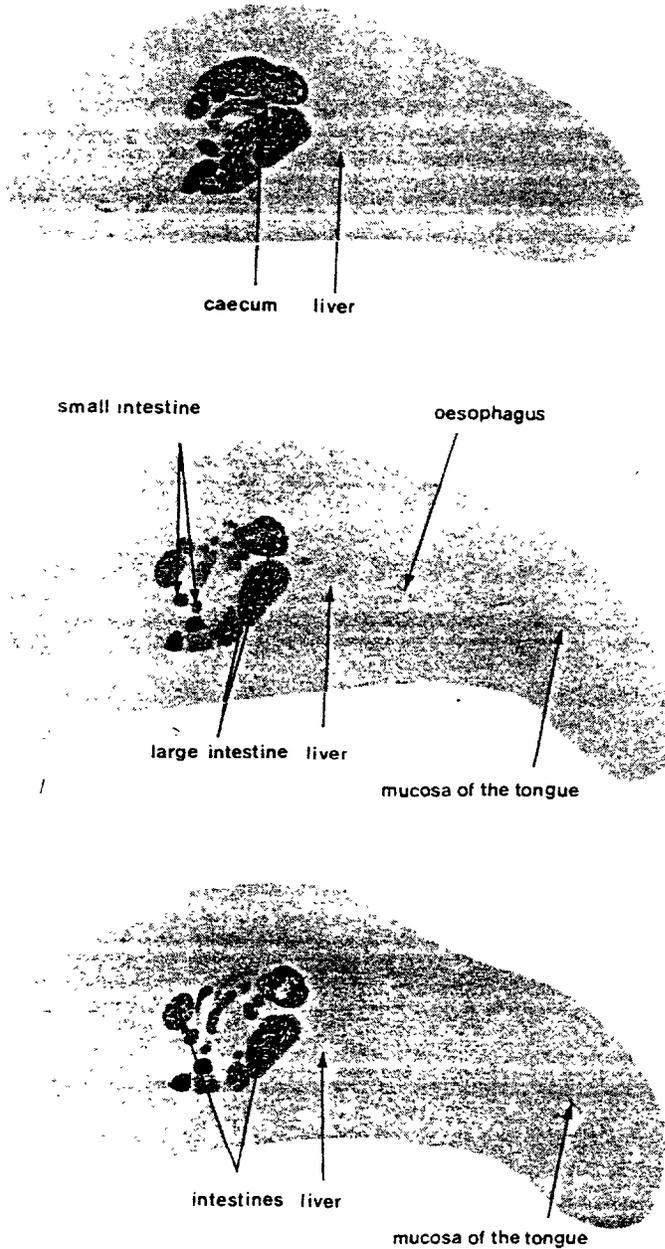


Fig. 13: Autoradiograms of sections of different body planes of a rat (R_{58}) 24 hrs after oral administration of 0.2 mg Octopirox- ^{14}C per kg body weight