ADME NTP Study S0028 o-Nitroanisole

The contract laboratory used the abbreviation ONA for the test article.
Sex/Species: adult male F344 rats
Vehicles: intravenous, ethanol:emulphlor:water (2:2:6); oral, ethanol:emulphlor (1:1); dermal, ethanol.

CASRN 91-23-6

Radiolabeled with carbon-14; [^{14}C]o-Nitroanisole

Studies Performed:

Oral

- Single 5 mg/kg oral gavage administration (low dose) to rats with sacrifice 7 days postdose.
- Single 25 mg/kg oral gavage administration (medium-low dose) to rats with sacrifice 7 days postdose.
- Single 50 mg/kg oral gavage administration (medium dose) to rats with sacrifice 7 days postdose.
- Single 500 mg/kg oral gavage administration (high dose) to rats with sacrifice 7 days postdose.

IV

- Single 25 mg/kg intravenous administration to rats with serial sacrifice at 5, 15, 30, 60 minutes; 1, 2, 4, 8, 12 hours, as well as at 1, 3, 5, and 7 days postdose (3 rats per time point).
- Single 25 mg/kg intravenous dose in rats with sacrifice 4.5 hours postdose (bile study; n = 2).

Dermal

- Single 20 mg/kg dermal dose to rats with covered dose site and sacrifice at 1, 2, 4, 8, and 12 hours as well as at 1 and 3 days postdose (3 rats per time point).

Toxicokinetics:

For dermal absorption following 20 mg/kg ONA administration, the rate of absorption appears to follow monophasic 1st order kinetics with a half-life of 20 hours. Due to large variation in the dose recovered after dermal exposure (recovery = 61.6 ± 17.8%), the absorption data was computed from urinary excretion data using the method of Wagner and Nelson (1964. J. Pharm. Sci. 53:1392). The equation used to determine absorption data was: % absorbed = $\{((1/K) \bullet (dXu/dt) + Xu)/(Xu)_\infty\} \bullet 100$ where K = urinary

elimination rate constant calculated from intravenous excreta data; dXu/dt = urinary excretion rate at time T; Xu = cumulative amount excreted in the urine at time T; and $(Xu)_\infty$ = cummulative amount eventually excreted in the urine. The concentration of ONA (as total ^{14}C) was determined in the blood, as well as urinary and fecal excretion profiles.

For ^{14}C equivalents concentration following intravenous administration (25 mg/kg), all tissues followed 1st order biphasic elimination kinetics and, together with urine and fecal elimination, fit the equation: $C = Ae^{-\alpha t} + Be^{-\beta t}$. The infinity minus method of data manipulation was employed prior to curve fitting. Kinetic constant definitions are found in Table 10c.

For the parent o-nitroanisole concentrations following intravenous administration: liver, kidney and small intestine best fit a monophasic 1st order elimination curve; skin and adipose tissue showed an uptake phase prior to parent elimination; and blood follows 1st order biphasic elimination. The elimination constants and kinetic equations are found in Tables 11a and b.

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Table 1. Percentage of dose and nmoles compound (as ^{14}C equivalents) found in excreta vs time from male Fisher 344 rats (n = 3) orally administered o-nitroanisole.

Low dose[a] (5 mg/kg)	Percent of Dose ± SD			nmoles ± SD		
Time (days)	Urine	Feces	Total	Urine	Feces	Total
1	73.29±12.24	1.48±1.34	74.77±11.97	4309±769	86±77	4395±745
2	1.93±0.72	3.44±0.97	5.37±1.61	114±44	203±63	316±103
3	1.55±0.89	0.29±0.03	1.84±0.86	90±49	17±2.0	107±47
4	0.76±0.31	0.12±0.04	0.88±0.34	44±19	8.2±2.4	53±21
5	0.34±0.18	0.08±0.03	0.42±0.22	20±11	4.5±2.2	24±14
6	0.37±0.24	0.06±0.04	0.44±0.27	22±15	3.6±2.1	25±17
7	0.23±0.07	0.10±0.08	0.33±0.14	14±3.8	6.2±5.1	20±8.8
Cumulative	78.48±11.00	5.58±0.34	84.06±10.69	4612±713	328±12	4939±701
Medium-Low dose (25 mg/kg)	Percent of Dose ± SD			nmoles ± SD		
Time (days)	Urine	Feces	Total	Urine	Feces	Total
1	76.75±2.81	4.89±0.58	81.64±3.23	25210±2173	1607±261	26817±2402
2	2.46±1.20	2.06±0.46	4.53±1.64	811±403	677±155	1488±555
3	0.78±0.36	0.16±0.02	0.93±0.38	253±120	51±72	304±124
4	0.62±0.13	0.17±0.12	0.79±0.25	202±41	56±40	258±82
5	0.42±0.22	0.19±0.15	0.62±0.28	138±74	66±53	204±97
6	0.26±0.10	0.10±0.09	0.36±0.18	87±30	32±28	118±57
7	0.83±0.37	0.23±0.22	1.06±0.59	271±121	74±74	345±194
Cumulative	82.12±3.91	7.80±0.81	89.93±4.72	26972±2431	2562±362	29534±2790

Table 1. Continued

Medium Dose[a] (50 mg/kg) Time (days)	Percent of Dose ± SD Urine	Feces	Total	nmoles ± SD Urine	Feces	Total
1	69.03±11.47	3.60±0.77	72.62±10.71	43212±4050	2296±679	45508±3371
2	1.23±0.19	2.44±1.11	3.67±1.19	775±132	1507±583	2282±577
3	0.41±0.10	0.26±0.08	0.67±0.18	256±47	162±38	418±85
4	0.64±0.23	0.22±0.02	0.86±0.23	399±115	139±4.9	538±112
5	0.17±0.10	0.08±0.04	0.26±0.08	104±52	53±24	157±36
6	0.27±0.06	0.05±0.01	0.32±0.06	167±33	35±4.9	202±38
7	0.10±0.02	0.09±0.02	0.20±0.02	64±18	57±16	121±25
Cumulative	71.85±11.81	6.75±0.60	78.60±12.19	44977±4092	4250±296	49227±3968
High Dose (500 mg/kg) Time (days)	Percent of Dose ± SD Urine	Feces	Total	nmoles ± SD Urine	Feces	Total
1	32.07±8.04	1.50±2.60	33.58±10.61	197944±55917	9564±16526	207507±72429
2	36.80±21.83	2.99±1.03	39.78±22.70	223422±129944	18301±6278	241722±135100
3	1.31±0.27	1.51±1.25	2.82±1.36	8063±1669	9064±7249	17127±7661
4	0.64±0.38	0.30±0.11	0.94±0.27	3932±2090	1874±744	5806±1371
5	0.16±0.02	0.10±0.04	0.26±0.06	960±108	629±223	1590±286
6	0.32±0.13	0.09±0.01	0.41±0.13	1943±700	530±43	2473±671
7	0.11±0.03	0.12±0.03	0.24±0.06	708±175	742±221	1450±357
Cumulative	71.40±14.41	6.62±0.78	78.02±13.65	436972±76459	40703±6123	477675±70395

[a] All doses include a ^{14}C tracer ≃ 50 μCi/kg.

Table 2. Summary of the percent dose recovered in tissues and excreta from rats (n=3) 7 days after oral administration of o-nitroanisole.

Tissue	Percent of Dose ± SD			
	Low (5 mg/kg)	Medium-Low (25 mg/kg)	Medium (50 mg/kg)	High (500 mg/kg)
Brain	0.0014 ± 0.0003	0.0021 ± 0.0016	0.0020 ± 0.0004	0.0023 ± 0.0009
Lung	0.0023 ± 0.0001	0.0029 ± 0.0005	0.0028 ± 0.0005	0.0027 ± 0.0007
Liver	0.0474 ± 0.0108	0.0439 ± 0.0057	0.0476 ± 0.0044	0.0367 ± 0.0051
Kidney	0.0117 ± 0.0016	0.0134 ± 0.0015	0.0098 ± 0.0005	0.0109 ± 0.0020
Spleen	0.0007 ± 0.0001	0.0012 ± 0.0004	0.0010 ± 0.0002	0.0042 ± 0.0018
Small Intestine	0.0062 ± 0.0012	0.0311 ± 0.0317	0.0028 ± 0.0010	0.0057 ± 0.0014
Fat	0.0115 ± 0.0017	0.0546 ± 0.0181	0.0274 ± 0.0114	0.0416 ± 0.0115
Testes	0.0011 ± 0.0010	0.0031 ± 0.0012	0.0010 ± 0.0001	0.0024 ± 0.0003
Muscle	0.0371 ± 0.0198	0.1479 ± 0.0045	0.0583 ± 0.0446	0.1571 ± 0.0803
Skin	0.0294 ± 0.0234	0.0439 ± 0.0079	0.0338 ± 0.0330	0.0293 ± 0.0066
Blood	0.0673 ± 0.0073	0.0777 ± 0.0054	0.0704 ± 0.0049	0.1897 ± 0.0447*
Plasma	0.0124 ± 0.0018	0.0246 ± 0.0122	0.0133 ± 0.0004	0.0161 ± 0.0022
Subtotal	0.216 ± 0.033	0.439 ± 0.018	0.246 ± 0.031	0.489 ± 0.127
Urine	78.48 ± 11.00	82.12 ± 3.91	71.85 ± 11.81	71.40 ± 14.41
Feces	5.58 ± 0.34	7.80 ± 0.81	6.75 ± 0.60	6.62 ± 0.78
Total	84.27 ± 10.69	90.37 ± 4.72	78.85 ± 12.19	78.51 ± 13.74

* Significantly different ($p < .05$) from other doses by one-way analysis of variance.

Table 3. Summary of nmoles o-nitroanisole (as ^{14}C-equivalents) recovered in tissues and excreta 7 days after oral administration.

Tissue	nmoles ± SD			
	Low (5.0 mg/kg)	Medium-Low (25 mg/kg)	Medium (50 mg/kg)	High (500 mg/kg)
Brain	0.08 ± 0.02	0.67 ± 0.51	1.28 ± 0.24	13.75 ± 5.29
Lung	0.14 ± 0.01	0.94 ± 0.22	1.79 ± 0.29	16.52 ± 4.15
Liver	2.80 ± 0.31	20.11 ± 3.03	23.28 ± 4.69	269.20 ± 27.3
Kidney	0.69 ± 0.08	4.40 ± 0.37	6.21 ± 0.80	67.17 ± 12.88
Spleen	0.04 ± 0.01	0.39 ± 0.11	0.65 ± 0.17	25.58 ± 11.31
Small Intestine	0.36 ± 0.06	10.13 ± 10.43	1.72 ± 0.52	35.04 ± 9.14
Fat	0.67 ± 0.08	18.11 ± 6.83	17.70 ± 8.78	254.20 ± 62.2
Testes	0.06 ± 0.06	1.02 ± 0.34	0.61 ± 0.09	14.96 ± 2.51
Muscle	2.20 ± 1.22	48.56 ± 3.63	38.26 ± 32.02	958.20 ± 485.2
Skin	1.75 ± 1.40	14.37 ± 2.35	20.25 ± 19.42	180.40 ± 45.8
Blood	3.94 ± 0.33	25.53 ± 3.00	44.62 ± 6.36	1166 ± 287.7
Plasma	0.73 ± 0.10	8.04 ± 3.90	8.40 ± 0.56	98.72 ± 13.96
Subtotal	12.73 ± 1.93	144.2 ± 5.91	164.8 ± 20.77	3100 ± 805
Urine	4612 ± 713	26972 ± 2431	44977 ± 4092	436972 ± 76459
Feces	328 ± 12	2562 ± 362	4250 ± 296	40703 ± 6123
Total	4952 ± 702	29678 ± 2796	49392 ± 3988	480775 ± 71200
nmoles Administered	5873 ± 163	32798 ± 1640	63125 ± 4985	614962 ± 24928

Table 4. Summary of percentage of dose and nmoles o-nitroanisole (as ^{14}C equivalents) excreted over time following iv administration of 25 mg/kg o-nitroanisole to male Fischer 344 rats (n=3).

Time (Days)	Urine		Feces		Total	
	% Dose ($\bar{x}$±SD)	nmoles ($\bar{x}$±SD)	% Dose ($\bar{x}$±SD)	nmoles ($\bar{x}$±SD)	% Dose ($\bar{x}$±SD)	nmoles ($\bar{x}$±SD)
1	81.61 ±3.62	43162 ±33003	7.70 ±0.20	2264 ±136	89.31 ±3.80	45425 ±32930
2	1.88 ±1.91	543 ±517	0.67 ±0.27	193 ±68	2.55 ±2.16	737 ±578
3	1.06 ±0.05	310 ±9	0.26 ±0.09	77 ±22	1.32 ±0.14	387 ±18
4	0.28 ±0.09	82 ±25	0.13 ±0.06	36 ±16	0.41 ±0.12	118 ±31
5	0.26 ±0.09	78 ±30	0.06 ±0.01	17 ±3	0.32 ±0.08	95 ±28
6	0.28 ±0.17	82 ±54	0.05 ±0.03	15 ±7	0.33 ±0.14	98 ±47
7	0.13 ±0.06	38 ±19	0.06 ±0.01	17 ±1	0.19 ±0.07	55 ±19
Cumulative	85.53 ±4.92	44295 ±33396	8.93 ±0.57	2619 ±108	94.46 ±5.49	46914 ±33433

Note: Most of the dose which was eliminated in the feces was excreted within 24 hrs after iv administration. In contrast, it took 48 hrs for maximal fecal excretion of this dose after oral administration (see Table 1, pg. 10).

Table 5. Summary of the % dose recovered in tissues and excreta vs time from rats (n=3) administered o-nitroanisole (25 mg/kg iv).

Time	5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr	12 hr	1 day	3 day	5 day	7 day
Tissue												
Brain	0.281 ±0.117	0.190 ±0.113	0.169 ±0.107	0.087 ±0.005	0.039 ±0.005	(0.024)	0.013 ±0.005	0.003 ±0.002	0.003 ±0.001	0.003 ±0.001	0.003 ±0.001	0.002 ±0.001
Lung	0.336 ±0.017	0.254 ±0.031	0.164 ±0.054	0.079 ±0.029	0.045 ±0.003	(0.027)	0.018 ±0.004	0.012 ±0.003	0.006 ±0.001	0.004 ±0.001	0.003 ±0.001	0.002 ±0.001
Liver	3.60 ±2.25	4.82 ±0.66	3.92 ±0.38	2.91 ±0.66	1.68 ±0.19	(0.585)	0.506 ±0.105	0.354 ±0.022	0.241 ±0.030	0.126 ±0.008	0.081 ±0.015	0.055 ±0.002
Kidney	1.65 ±0.04	2.83 ±0.24	2.61 ±1.23	1.40 ±0.17	0.647 ±0.067	(0.261)	0.109 ±0.014	0.063 ±0.005	0.041 ±0.009	0.023 ±0.002	0.018 ±0.002	0.015 ±0.002
Spleen	0.133 ±0.019	0.059 ±0.014	0.088 ±0.012	0.038 ±0.005	0.019 ±0.003	(0.010)	0.006 ±0.001	0.003 ±0.001	0.003 ±0.001	0.002 ±0.001	0.002 ±0.001	0.001 ±0.0005
Small Intestine	1.21 ±0.38	1.85 ±0.92	1.66 ±0.72	2.43 ±1.26	2.77 ±1.46	(0.754)	0.145 ±0.071	0.048 ±0.009	0.023 ±0.006	0.009 ±0.004	0.009 ±0.006	0.004 ±0.002
Adipose Tissue*	2.55 ±1.52	6.75 ±5.68	16.2 ±11.4	4.70 ±1.39	3.68 ±1.13	(2.16)	0.244 ±0.087	0.146 ±0.132	0.048 ±0.015	0.055 ±0.026	0.041 ±0.014	0.035 ±0.012
Testes	0.387 ±0.013	0.391 ±0.063	0.359 ±0.054	0.196 ±0.036	0.079 ±0.016	(0.033)	0.022 ±0.004	0.010 ±0.001	0.005 ±0.001	0.003 ±0.001	0.003 ±0.002	0.003 ±0.0005
Muscle	25.97 ±4.09	19.52 ±2.58	16.5 ±3.3	8.80 ±3.26	3.30 ±0.74	(1.37)	0.614 ±0.119	0.305 ±0.084	0.144 ±0.028	0.095 ±0.006	0.093 ±0.025	0.075 ±0.011
Skin	7.71 ±2.87	10.27 ±2.95	12.7 ±7.9	4.28 ±1.08	1.88 ±0.45	(0.841)	0.597 ±0.471	0.157 ±0.035	0.083 ±0.018	0.061 ±0.009	0.065 ±0.029	0.056 ±0.023
Blood	8.81 ±0.97	6.51 ±1.72	5.29 ±0.24	3.70 ±0.36	1.86 ±0.12	(0.815)	0.477 ±0.052	0.359 ±0.013	0.238 ±0.028	0.167 ±0.022	0.142 ±0.029	0.135 ±0.013
Plasma	2.84 ±0.29	3.13 ±0.65	2.31 ±0.40	1.94 ±0.24	1.00 ±0.05	(0.382)	0.226 ±0.016	0.131 ±0.007	0.065 ±0.019	0.022 ±0.006	0.018 ±0.003	0.012 ±0.001

Table 5.--Continued.

Time Tissue	5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr	12 hr	1 day	3 day	5 day	7 day
Urine and Bladder contents	0.061 (n=1)	4.08 ±2.03	18.2 ±2.43	53.8 ±5.75	47.37 ±7.09	(96.8)	92.0 ±17.3	93.1 ±4.7	86.0 ±6.95	83.1 ±6.96	93.3 ±18.3	85.5 ±4.88
Feces and Intestinal contents	0.797 ±0.195	2.07 ±0.66	3.13 ±0.44	6.10 ±0.93	13.0 ±2.87	(8.14)	8.25 ±2.35	7.47 ±1.77	7.30 ±0.76	9.35 ±1.09	8.09 ±6.82	8.93 ±0.57
Injection sites	6.56 ±3.23	0.985 ±0.058	3.39 ±0.22	3.11 ±1.11	2.78 ±1.52	(0.219)	0.138 ±0.115	0.311 ±0.45	0.024 ±0.006	0.015 ±0.014	0.061 ±0.036	0.095 ±0.037
Total % dose recovered	59.97 ±5.83	60.57 ±9.54	84.51 ±18.45	91.59 ±6.00	79.15 ±8.32	(111)	103 ±15	102 ±4.4	94.2 ±6.4	93.0 ±7.2	102 ±11.6	95.0 ±5.5

Values in parentheses are the average of 2 rats.

* Adipose tissue values are calculated from the concentration of dose in renal fat.

Note: Individual animal data is given in Tables 10-22.

Table 6. Summary of nmoles (as ^{14}C equivalents) recovered in tissues vs time from rats (n=3) administered o-nitroanisola (25 mg/kg iv).

Time	5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr	12 hr	1 day	3 day	5 day	7 day
Tissue												
Brain	85 ±39	59 ±39	47 ±30	26 ±3	12 ±0	(7)	3.4 ±1.0	0.9 ±0.5	0.9 ±0.2	0.9 ±0.3	0.9 ±0.5	0.50 ±0.16
Lung	101 ±11	73 ±2	45 ±15	23 ±7	13 ±1	(8)	5.0 ±0.7	3.2 ±0.7	1.9 ±0.6	1.0 ±0.2	1.2 ±0.2	0.61 ±0.24
Liver	1065 ±667	1475 ±324	1083 ±44	878 ±270	527 ±137	(175)	144 ±37	94 ±3.9	75 ±9.5	37 ±2.4	26 ±0.9	16 ±1.3
Kidney	492 ±35	858 ±39	716 ±332	418 ±60	202 ±48	(76)	31 ±5.2	16 ±0.8	13 ±2.7	6.9 ±0.5	6.0 ±1.4	4.3 ±0.4
Spleen	40 ±6.7	18 ±4	24 ±4	11 ±2	6 ±1	(3)	1.5 ±0.3	0.8 ±0.2	0.8 ±0.1	0.4 ±0.1	0.5 ±0.2	0.29 ±0.12
Small Intestine	363 ±118	560 ±292	463 ±204	708 ±328	822 ±381	(221)	42 ±22	13 ±2	7.0 ±1.8	2.6 ±1.2	2.6 ±1.1	1.1 ±0.5
Adipose Tissue*	769 ±485	2114 ±1923	4469 ±3116	1422 ±489	1163 ±453	(643)	71 ±32	40 ±37	15 ±4.5	16 ±7.6	13 ±2.1	10 ±3.8
Testes	116 ±111	118 ±9.4	100 ±15	59 ±13	25 ±8	(10)	6.2 ±1.5	2.7 ±0.4	1.6 ±0.4	0.9 ±0.4	0.9 ±0.3	0.97 ±0.17
Muscle	7734 ±856	5987 ±1337	4568 ±1033	2631 ±964	1028 ±279	(400)	176 ±51	81 ±21	45 ±8.6	28 ±1.9	30 ±5.8	22 ±4.2
Skin	2273 ±686	3201 ±1217	3549 ±2311	1300 ±438	598 ±229	(241)	176 ±154	42 ±9	26 ±5.5	18 ±2.5	20 ±4.6	16 ±7.3
Blood	2643 ±375	2014 ±705	1471 ±149	1114 ±198	580 ±118	(240)	135 ±24	96 ±3	74 ±8.6	49 ±6.5	46 ±4.3	39 ±6.0
Plasma	854 ±136	964 ±283	643 ±140	583 ±112	311 ±49	(112)	64 ±9.3	35 ±3	20 ±6	6.3 ±1.8	6.0 ±1.7	3.4 ±0.5

Values in parentheses are the average of 2 rats.

*Adipose tissue values are calculated from the concentration of dose in renal fat.

Table 7. Summary of tissue (g):blood (ml) ratios ±S.D. following administration of o-nitroanisole (25 mg/kg iv) to rats (n=3).

Time	5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr	12 hr	1 day	3 day	5 day	7 day
Tisue												
Brain	0.30 ±0.14	0.29 ±0.21	0.26 ±0.16	0.20 ±0.02	0.19 ±0.01	(0.26)	0.22 ±0.06	0.07 ±0.03	0.12 ±0.02	0.15 ±0.01	0.17 ±0.09	0.11 ±0.05
Lung	0.59 ±0.08	0.61 ±0.11	0.46 ±0.17	0.33 ±0.12	0.40 ±0.07	(0.46)	0.54 ±0.08	0.42 ±0.05	0.41 ±0.10	0.28 ±0.04	0.37 ±0.03	0.23 ±0.09
Liver	0.74 ±0.43	1.41 ±0.14	1.52 ±0.23	1.49 ±0.16	1.73 ±0.08	(2.31)	2.04 ±0.22	1.55 ±0.16	1.82 ±0.17	1.28 ±0.26	1.00 ±0.15	0.77 ±0.12
Kidney	1.82 ±0.06	4.35 ±1.05	4.79 ±2.18	3.78 ±0.46	3.51 ±0.20	(3.27)	2.18 ±0.09	1.53 ±0.15	1.71 ±0.28	1.26 ±0.25	1.19 ±0.32	1.01 ±0.12
Spleen	0.50 ±0.01	0.31 ±0.06	0.53 ±0.03	0.33 ±0.03	0.31 ±0.04	(0.38)	0.36 ±0.05	0.28 ±0.09	0.37 ±0.07	0.28 ±0.03	0.32 ±0.06	0.26 ±0.08
Small Intestine	0.49 ±0.08	0.95 ±0.31	1.36 ±0.20	2.52 ±1.48	5.76 ±3.20	(3.93)	1.11 ±0.43	0.40 ±0.08	0.41 ±0.11	0.18 ±0.11	0.18 ±0.08	0.10 ±0.04
Adipose Tissue*	0.39 ±0.26	1.46 ±1.30	3.98 ±2.89	1.61 ±0.36	2.55 ±0.80	(3.39)	0.67 ±0.27	0.53 ±0.49	0.25 ±0.06	0.43 ±0.21	0.36 ±0.05	0.33 ±0.09
Testes	0.29 ±0.03	0.41 ±0.11	0.43 ±0.06	0.34 ±0.05	0.30 ±0.07	(0.27)	0.29 ±0.02	0.18 ±0.02	0.14 ±0.01	0.12 ±0.05	0.15 ±0.05	0.15 ±0.03
Muscle	0.53 ±0.08	0.57 ±0.16	0.56 ±0.14	0.43 ±0.20	0.32 ±0.08	(0.30)	0.23 ±0.04	0.15 ±0.04	0.11 ±0.01	0.10 ±0.01	0.12 ±0.03	0.10 ±0.01
Skin	0.50 ±0.21	0.91 ±0.28	0.75 ±0.78	0.64 ±0.10	0.57 ±0.11	(0.58)	0.73 ±0.61	0.24 ±0.05	0.20 ±0.06	0.21 ±0.05	0.25 ±0.06	0.23 ±0.09

Values in parentheses are the average of 2 rats.

* Adipose tissue values are calculated from the concentration of dose in renal fat.

Table 8. Percentage of dose (as total ^{14}C and parent) excreted in bile after o-nitroanisole (ONA) (25 mg/kg, iv).

	% dose as ^{14}C			% dose as ONA		
Rat:	A	B	avg.	A	B	avg.
Time (Hour)						
0.25	0.147	0.838	0.493			
0.50	0.404	1.422	0.913	0.0158	0.1506	0.0832
0.75	0.456	1.059	0.757			
1.0	0.589	0.940	0.764			
1.25	0.517	0.792	0.655			
1.50	0.389	0.774	0.582	0.0175	0.0299	0.0237
1.75	0.475	0.629	0.552			
2.0	0.433	0.570	0.501			
2.25	0.477	0.403	0.440			
2.50	0.622	0.374	~0.342	0.0118	0.0107	0.0113
2.75		0.334	~0.322			
3.0	0.217	0.272	0.245			
3.25	0.225	0.245	0.235			
3.50	0.217	0.183	0.200	5.51×10^{-3}	5.58×10^{-3}	5.55×10^{-3}
3.75	0.180	0.155	0.168			
4.0	0.158	0.163	0.160			
4.25	0.269	0.126	~0.130	1.94×10^{-3}	2.39×10^{-3}	2.17×10^{-3}
4.50		0.131	~0.133			
Cumulative % dose	5.775	9.410	7.593	0.0526	0.1992	0.1259

Table 9. o-Nitroanisole Dermal Recoveries ($\bar{x}$ ± SD). Percent of Dose (20 mg/kg, topical).

	(n=3) 1 hr	(n=3) 2 hr	(n=3) 4 hr	(n=4) 8 hr	(n=4) 12 hr	(n=3) 1 day	(n=3) 3 day
Urine	0.80 ±0.60	6.56 ±3.22	8.50 ±1.57	22.92 ±11.02	34.93 ±14.48	45.30 ±3.46	69.63 ±3.13
Feces	0.052 ±0.007	0.389 ±0.179	0.866 ±0.148	2.27 ±0.37	1.21 ±0.28	2.20 ±0.71	5.52 ±2.05
Exposure Site	58.18 ±12.59	32.58 ±16.02	64.63 ±7.72	35.23 ±26.16	8.71 ±4.06	20.82 ±6.39	1.32 ±0.29
Blood	0.229 ±0.026	0.258 ±0.116	0.199 ±0.009	0.448 ±0.227	0.432 ±0.305	0.268 ±0.067	0.99 ±0.16
Skin	0.83 ±0.60	0.83 ±0.38	0.89 ±0.04	2.10 ±1.91	1.89 ±1.87	2.18 ±0.20	1.36 ±1.46
Total Recovered	60.10 ±12.38	40.61 ±18.08	75.09 ±6.41	62.96 ±21.15	47.16 ±15.88	70.77 ±3.41	78.83 ±2.17

Table 10a. Elimination constants for o-nitroanisole (as ^{14}C equivalents) from tissues following iv administration (25 mg/kg).

Organ	A	B	α	β	r	$t_{1/2}$ (hr) α	$t_{1/2}$ (hr) β
Blood[a]	7.28 ±0.91	0.322 ±0.043	0.703 ±0.089	0.0064 ±0.0015	0.990	0.986 ±0.125	108.3 ±25.38
Plasma	2.78 ±0.69	0.081 ±0.026	0.484 ±0.112	0.0124 ±0.0033	0.992	1.433 ±0.331	55.89 ±14.87
Liver	5.27 ±0.71	0.361 ±0.041	0.727 ±0.096	0.0121 ±0.0013	0.999	0.953 ±0.126	57.27 ±6.15
Brain	0.154 ±0.038	0.00299 ±0.00046	0.523 ±0.115	0.00128 ±0.00066	0.957	1.326 ±0.293	541.4 ±279.2
Lung	0.255 ±0.055	0.0107 ±0.0022	0.991 ±0.199	0.0111 ±0.0020	0.981	0.699 ±0.140	62.43 ±11.25
Spleen	0.0699 ±0.0132	0.00302 ±0.00042	0.595 ±0.098	0.00558 ±0.00166	0.926	1.165 ±0.193	124.2 ±36.9
Testes	0.387 ±0.080	0.00578 ±0.00135	0.670 ±0.109	0.00468 ±0.00126	0.990	1.035 ±0.169	148.1 ±39.9
Muscle	21.49 ±4.97	0.207 ±0.056	0.815 ±0.144	0.00712 ±0.00311	0.991	0.850 ±0.150	97.33 ±42.51
Kidney	2.35 ±0.37	0.056 ±0.013	0.551 ±0.080	0.0089 ±0.0022	0.993	1.258 ±0.183	77.88 ±19.25
Small Intestine	2.42 ±0.52	0.024 ±0.011	0.350 ±0.053	0.010 ±0.0042	0.988	1.980 ±0.300	69.32 ±29.11
Fat	7.75 ±1.15	0.0581 ±0.0172	0.430 ±0.034	0.0028 ±0.0032	0.993	1.612 ±0.127	247.5 ±282.8
Skin	8.10 ±2.11	0.104 ±0.037	0.598 ±0.132	0.0043 ±0.0038	0.920	1.159 ±0.256	161.2 ±142.0

[a] All tissues fit the equation: $C = Ae^{-\alpha t} + Be^{-\beta t}$.

Table 10b. Elimination constants for o-nitroanisole (as ^{14}C equivalents) from excreta following iv administration (25 mg/kg).

	A	B	α	β	r	$t_{1/2}$ (hr) α	$t_{1/2}$ (hr) β
Urine	79.56 ±15.27	7.68 ±1.28	0.477 ±0.170	0.028 ±0.002	.999	1.45 ±0.52	25.0 ±1.8
Feces	8.35 ±1.50	1.14 ±0.17	1.50 ±0.32	0.020 ±0.002	.994	0.46 ±0.10	34.5 ±3.5

Urine and feces fit the equation: $C = Ae^{-\alpha t} + Be^{-\beta t}$.

Note: The infinity minus method of data manipulation was employed prior to curve fitting (see Fig. 20 and 21, pg. 82-83).

Table 10c. Definition of kinetic constants.

C	Concentration of total ^{14}C in tissues
t	Time
A	Constant for initial elimination phase
α	First-order decay rate constant for initial elimination phase
B	Constant for terminal elimination phase
β	First-order decay rate constant for terminal elimination phase
r	Correlation coefficient

Table 11a. Elimination constants for parent o-nitroanisole from selected tissues and excreta following iv administration (25 mg/kg).

Organ	A	B	α	β	r	$t_{1/2}$ (hr) α	$t_{1/2}$ (hr) β
Blood	7.415 ±0.480	0.353 ±0.091	1.319 ±0.087	0.315 ±0.026	1.00	0.525 ±0.035	2.200 ±0.182
Skin	17.61 ±8.04	--	7.85 ±4.40	1.782 ±0.330	0.982	0.088 ±0.049	0.389 ±0.072
Fat	6.64 ±1.46	--	6.46 ±2.21	0.348 ±0.087	0.925	0.108 ±0.037	1.99 ±0.50
Kidney	0.763 ±0.11	--	1.27 ±0.079	--	0.992	0.546 ±0.034	--
Liver	1.44 ±0.26	--	2.03 ±0.096	--	0.996	0.341 ±0.016	--
Small Intestine	1.13 ±0.15	--	1.03 ±0.071	--	0.991	0.673 ±0.046	--
Urine *	0.415 ±0.036	--	0.194 ±0.055	--	0.934	3.57 ±1.01	--

*The infinity minus method of data manipulation was used on urinary data prior to curve fitting (see Fig. 20, pg. 82).

Table 11b. Kinetic equations for parent o-nitroanisole.

Organ	Equation
Blood	$C = Ae^{-\alpha t} + Be^{-\beta t}$
Skin Fat	$C = A(e^{-\alpha t} - e^{-\beta t})$
Kidney Liver Small Intestine Urine	$C = Ae^{-\alpha t}$