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Disposition of Dapsone and Monoacetyldapsone in Rats[1] (39062)

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From the time that the noncultivable *Mycobacterium leprae* was grown in mouse foot pads (1, 2), this rodent has been used widely for testing the activity of drugs against *M. leprae* and as the basis for laboratory studies of human leprosy (3). By the mouse foot pad test system, dapsone (4,4′-diaminodiphenyl sulfone, DDS), the most widely used drug for the treatment of human leprosy (4), was found to inhibit multiplication of *M. leprae* in mice exhibiting plasma levels of 1–10 ng DDS/ml (5). The lower limit of this range was obtained by extrapolation and must be considered tentative.

Previously, the disposition of DDS in mice (6) and human subjects (7) was examined to assess the value of the mouse as a model of man. Those studies showed that mice differed markedly from man in regard to the acetylation of DDS to monoacetyl DDS (MADDS), the deacetylation of MADDS to DDS, and the rate of clearance of DDS from the circulation. The only similarity between the two species was the extent of binding of DDS by plasma proteins. Thus, the mouse proved of little value as a model of man for studies on the disposition of DDS.

A further disadvantage of the mouse test system is the limited multiplication of *M. leprae* in the foot pad. Other rodents have been tested (8, 9), but were not found to be superior to the mouse. More recently, Buffalo and Lewis rats that were neonatally thymectomized or treated with antithymocytic serum demonstrated greater multiplication of *M. leprae* in the foot pads (10, 11). The Lewis strain was more susceptible (10). Because rats may offer certain advantages over mice for long-term studies on the multiplication of *M. leprae* and may provide a better model of man in regard to the disposition of DDS, we conducted studies on the metabolism of both DDS and MADDS in intact and neonatally thymectomized rats. At the time our studies were initiated, the only report of studies of DDS in rats was that of Satake (12), who found that rat liver homogenates acetylated DDS to MADDS and deacetylated MADDS to DDS.

In our study, we measured the plasma levels of DDS and MADDS at a sufficient number of time periods after the administration of each drug to estimate the half-times of disappearance ($T_{1/2}$) of the drugs. Also, the extent of plasma protein binding of the two compounds was measured both *in vivo* and *in vitro*.

Methods. The DDS, MADDS, and 4,4′-diacetyl DDS (DADDS) used in these studies were described previously (13). Buffalo and Lewis rats were obtained from Simonsen Laboratories, Gilroy, California, and the thymectomized rats were prepared as described previously (10). Male rats ranged in weight from 351 to 405 g and females from 190 to 237 g. For administration, DDS was dissolved in a mixture of polyethylene glycol 200 and 0.9% saline (1:1, v/v). The concentrations were 0.5 mg/ml for doses of 1.0 mg/kg, and 1.25 mg/ml for doses of 5.0 mg/kg. Equimolar solutions of MADDS were similarly prepared and both drugs were administered ip. In the experiments using Buffalo rats, all animals were administered the drugs only once and they were sacrificed at the end of the experiment. Drug levels in

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TABLE I. PLASMA LEVELS OF DDS AND MADDS IN RATS RECEIVING DDS.

Study, strain, and sex[a]	Sampling time (hr)	Mean (± SE) plasma level (ng/ml)		Mean (± SE) % MADDS of total drug[b]	$T_{1/2}$ of DDS[c] (hr)
		DDS	MADDS		
I, Buffalo, 12♀	2	527 ± 35	375 ± 30	38 ± 1	6.8
	4	397 ± 25	455 ± 28	50 ± 1	(4.2–18.0)
	6	242 ± 21	363 ± 14	56 ± 1	
	8	313 ± 7	480 ± 30	57 ± 2	
II, Buffalo, 12♂	2	232 ± 15	27 ± 2	9 ± 0	5.1
	4	167 ± 17	30 ± 6	13 ± 1	(4.0–6.8)
	6	154 ± 9	34 ± 2	17 ± 1	
	8	96 ± 6	28 ± 0	20 ± 1	
III, Buffalo, 4♀[d]	2	535 ± 24	414 ± 13	40 ± 1	6.5
	4	351 ± 28	494 ± 26	55 ± 1	(4.9–9.6)
	6	296 ± 16	508 ± 23	60 ± 1	
	8	276 ± 12	522 ± 26	62 ± 1	
IV, Buffalo, 12♀[e]	2	2990 ± 300	2130 ± 250	38 ± 3	5.7
	4	2110 ± 130	2660 ± 220	52 ± 3	(4.2–9.1)
	6	1580 ± 150	2420 ± 180	57 ± 1	
	8	1470 ± 110	2350 ± 80	58 ± 1	
V, Lewis, 5♀	2	818 ± 21	454 ± 24	32 ± 1	6.7
	4	610 ± 13	469 ± 20	40 ± 1	(5.7–8.2)
	6	489 ± 25	408 ± 6	42 ± 1	
	8	444 ± 14	394 ± 11	43 ± 1	
VI, Lewis, 6♂	2	205 ± 11	63 ± 3	21 ± 1	5.0
	4	126 ± 8	47 ± 3	24 ± 1	(4.0–6.6)
	6	117 ± 10	39 ± 3	22 ± 1	
	8	84 ± 4	31 ± 2	24 ± 1	

[a] In studies I, II, and IV, three rats were sacrificed at each time period. In the other studies, each animal was bled at each time, nonterminally, as described in the methods. All rats received 1.0 mg DDS/kg, intraperitoneally, unless otherwise noted.

[b] MADDS (as DDS equivalents) × 100/DDS + MADDS.

[c] Half-lives were calculated from regression lines as described in the text. The 95% confidence limits are shown in parenthesis.

[d] Animals were neonatally thymectomized.

[e] The dose was 5.0 mg DDS/kg, intraperitoneally.

Buffalo rats (Tables I and II) were determined in plasma samples prepared from heparinized blood obtained by direct heart puncture (under ether anesthesia) with the exception of the male rats and thymectomized female rats in Table I. In the latter two studies, the plasma data were obtained from heparinized blood samples collected by a nonterminal orbital sinus bleeding technique (14). In plasma prepared from heart blood samples, the levels of DDS and MADDS were determined by a fluorometric procedure that measures DDS and MADDS in the same extract (13). These extracts were also examined for the presence of other DDS metabolites by thin-layer chromatographic procedures (13). DDS and MADDS were recovered quantitatively following incubation with plasma or red blood cells (4 hr, 25°) from untreated rats, indicating that these tissues did not metabolize the drugs.

Drug levels in plasma obtained from orbital blood samples were measured by a more sensitive chromatographic–fluorometric procedure (15). Previous work in our laboratories demonstrated that the direct fluorometric (13) and the chromatographic–fluorometric (15) methods yielded the same results. However, because of the increased sensitivity of the latter method, a considerably smaller sample size is required. To assess possible differences in levels of drugs in blood

TABLE II. PLASMA LEVELS OF DDS AND MADDS IN RATS RECEIVING MADDS.

Study, strain, and sex[a]	Sampling time (hr)	Mean (± SE) plasma level (ng/ml)		Mean (± SE) % DDS of total drug[b]	$T_{1/2}$ of MADDS[c] (hr)
		MADDS	DDS		
VII, Buffalo, 12♀	2	1300 ± 118	237 ± 7	18 ± 2	5.5
	4	1020 ± 71	262 ± 13	23 ± 1	(4.1–8.2)
	6	735 ± 38	273 ± 35	30 ± 2	
	8	620 ± 54	268 ± 48	33 ± 2	
VIII, Buffalo, 12♀[d]	2	8080 ± 240	1100 ± 18	14 ± 1	3.8
	4	6190 ± 380	1110 ± 30	17 ± 1	(3.0–5.2)
	6	4440 ± 480	1180 ± 70	24 ± 1	
	8	2770 ± 380	1200 ± 80	34 ± 4	
IX, Lewis, 5♀	2	1496 ± 134	536 ± 25	30 ± 2	3.4
	4	778 ± 87	522 ± 26	45 ± 2	(2.8–4.5)
	6	508 ± 48	459 ± 35	51 ± 1	
	8	444 ± 25	425 ± 26	53 ± 2	
X, Lewis, 6♂	2	345 ± 35	118 ± 6	30 ± 2	1.9
	4	130 ± 15	105 ± 7	49 ± 2	(1.7–2.2)
	6	68 ± 9	75 ± 7	57 ± 3	
	8	39 ± 2	61 ± 4	65 ± 2	

[a] In studies VII and VIII, three rats were sacrificed at each time period. Each rat in other studies was bled nonterminally at each time, as described in the methods. All rats received 1.2 mg MADDS/kg, intraperitoneally, unless otherwise noted.

[b] DDS × 100/DDS + MADDS (as DDS equivalents).

[c] Half-lives were calculated from regression lines as described in the text. The 95% confidence limits are shown in parenthesis.

[d] The dose was 5.8 mg MADDS/kg, intraperitoneally.

obtained from the heart or from the orbital sinus, we utilized the male Buffalo rats of Table I receiving DDS. Immediately after obtaining a blood sample from the orbital sinus, each rat was bled terminally from the heart. Plasma drug levels were then determined by the chromatographic–fluorometric method. DDS levels in samples from the orbital sinus averaged 93.6% of the levels in plasma from heart blood; MADDS levels averaged 89.6%.

Using the nonterminal orbital sinus bleeding technique, we studied DDS and MADDS disposition in Lewis rats (Tables I and II) in a cross-over design, allowing a one-month rest between the two drug treatments.

In all experiments, blood samples were obtained at 2, 4, 6, and 8 hr after treatment. The number of animals used in each study is shown in the tables. To calculate $T_{1/2}$ values, all levels of the administered drug in the animals of each study were used to obtain regression lines of the logarithmic decay of the compound with time. All regression lines exhibited correlation coefficients that indicated the slopes were significantly different from zero. $T_{1/2}$ values calculated from the regression equations obtained in the various studies were compared by testing for significant differences between the slopes of the regression lines (16).

Studies of plasma protein binding of DDS and MADDS were performed by an ultrafiltration technique (17). Binding *in vivo* was measured in heparinized plasma from female Buffalo rats receiving ip, either DDS or MADDS. *In vitro* binding was determined in plasma from control animals, and in this plasma diluted to a protein concentration of 10 mg/ml with 0.1 *M* phosphate buffer, pH 7.4. The final concentration of added DDS or MADDS was 2.0 μg/ml in both *in vitro* studies. Protein concentrations were determined spectrophotometrically (18).

Results. Columns 3 and 4 of Table I present the mean values of DDS and MADDS found in the rats receiving DDS. Comparisons of the levels of DDS and MADDS at the various times in the two sexes of the Buffalo (Studies I and II) and Lewis rats

(Studies V and VI) receiving 1.0 mg DDS/kg show that female rats exhibited consistently and significantly higher ($P < 0.05$) levels of both compounds. That the difference between sexes was greater in the levels of MADDS is emphasized by the calculated mean percentage MADDS of the total measured drug at each time period shown in column 5. In both strains, female rats exhibited higher ($P < 0.05$) percentages than did male rats. Interestingly, this percentage increased with time in both sexes. It was 32–38% at 2 hr and increased to 43–57% at 8 hr in female rats. In male rats, it was 9–21% at 2 hr and increased to 20–24% by 8 hr. Clearly, both sexes of both strains were capable of acetylating DDS, with females apparently showing a greater capacity for this conjugation.

Differences between the two strains were also apparent. Female Lewis rats (Study V) exhibited significantly higher ($P < 0.001$) levels of DDS and lower ($P < 0.01$) percentages MADDS of total drug at all times than did female Buffalo rats (Study I). Male Lewis rats (Study VI) exhibited significantly lower ($P < 0.05$) levels of DDS only at 4 hr, higher ($P < 0.02$) levels of MADDS at 2 and 4 hr, and significantly higher ($P < 0.05$) percentages as MADDS at all times than did male Buffalo rats (Study II).

Thymectomized Buffalo female rats (Study III) did not differ consistently from intact female rats of this strain (Study I) in regard to any parameter measured or calculated. Only the 6-hr MADDS levels in the rats of Study III were significantly higher ($P < 0.005$) than those of Study I. Also, the percentages as MADDS were significantly higher ($P < 0.02$) at only 4 and 6 hr in the thymectomized rats. Increasing the dose from 1.0 (Study I) to 5.0 mg DDS/kg in female Buffalo rats (Study IV) resulted in proportionate increases in levels of DDS and MADDS, but there was no effect on the percentage as MADDS at any time.

Calculated $T_{1/2}$ values of DDS are shown in the last column of this table. All groups showed similar values; none was significantly different from any other. Thus, although numerous differences between sexes and strains were noted as described above, the differences were not reflected in clearance rates of DDS.

An assessment of the capability of rats to deacetylate MADDS following the administration of this compound yielded the results shown in Table II. In all groups, MADDS was readily deacetylated as indicated by the levels of DDS found at all times. Again, female Lewis rats (Study IX) exhibited significantly higher ($P < 0.001$) levels of both MADDS and DDS than did males (Study X) at all times. In this case however, differences in the extent of deacetylation as shown by the calculated mean percentages DDS of total drug (column 5) were significant ($P < 0.05$) only at 6 and 8 hr. Strain differences were again apparent. Female Buffalo rats (Study VII) exhibited significantly higher ($P < 0.02$) levels of MADDS at 6 and 8 hr than did Lewis rats (Study IX), but lower ($P < 0.02$) levels of DDS at all times. The mean percentage DDS of the total drug was lower ($P < 0.01$) at all times in the Buffalo compared with the Lewis female rats. No studies of male Buffalo rats receiving MADDS were performed. Female rats of this strain receiving a higher dose of MADDS (Study VIII) exhibited correspondingly higher levels of MADDS and DDS, but the mean percentage DDS of total drug was not consistently different from that observed at the lower dose (Study VII). Again, in all studies of Table II, an increase in the percentage of the product, DDS, was noted with time, similar to the temporal increase in the percentage of the product, MADDS, after administering DDS in the studies of Table I.

As shown in the last column of Table II, the $T_{1/2}$ of the administered drug in the female Buffalo rats receiving the two doses was similar. The slopes of the two regression lines were not significantly different. However, in Lewis rats, the calculated $T_{1/2}$ value for MADDS was significantly shorter in male than in female rats. Furthermore, both sexes of the Lewis strain exhibited shorter $T_{1/2}$ values for MADDS than for DDS (Table I). Comparable differences were not noted in the Buffalo strain.

That the metabolic disposition of DDS may be different from that of MADDS is suggested by comparing the administered drug

levels in Tables I and II. Although both strains of rats received equimolar doses of each drug, we found that DDS levels after DDS (column 3 of Table I) were considerably lower at the early time periods than MADDS levels after MADDS (column 3 of Table II). This was a consistent finding regardless of the sex, strain of rat, or dose of drug.

The presence in plasma extracts of DDS and MADDS after DDS administration and MADDS and DDS after MADDS administration was confirmed by thin-layer chromatography. Only two blue fluorescent spots were visible under ultraviolet light; they gave positive color tests with the *p*-dimethylaminobenzaldehyde spray reagent and exhibited R_f values identical to authentic DDS and MADDS. No evidence was obtained either by the chromatographic–fluorometric procedure or by thin-layer chromatography that suggested the presence of the diacetylated derivative, DADDS.

It is clear from the above that following administration of DDS and MADDS, conversion of one compound to the other occurs. By analogy with other studies (19), it must be presumed that the two reactions of acetylation and deacetylation are operating concurrently when either DDS or MADDS is administered. Our approach to illustrating this phenomenon is shown in Fig. 1. Therein, we have plotted the mean percentage MADDS of total drug versus time in both sexes of Lewis rats receiving equimolar doses of DDS and MADDS. The values after DDS injection are those of column 5 of Table I, and the values after MADDS administration are those of column 5 of Table II subtracted from 100%. By this means, we can compare results of the two administrations on the same basis. As shown in the figure, the two curves for female rats (open circles) converge to approximately the same value (43–47%) by 8 hr following injection of the two drugs. This convergence we interpret to represent an approach to a steady state of acetylation–deacetylation in this sex. In male rats (solid circles), the convergence is not as complete at the last blood sampling time of 8 hr as in the females. Nevertheless, the plot suggests that a steady state between 24 and 35% MADDS is being approached. It is clear that the steady state point would be lower in the male than in the female rats. This figure also reemphasizes the conclusion made from data of Tables I and II that the two sexes differ more in the extent of acetylation than of deacetylation when one compares the relative distances between the two dashed and the two solid lines. This suggests that the steady state of acetylation–deacetylation is controlled more by the extent of acetylation than by that of deacetylation.

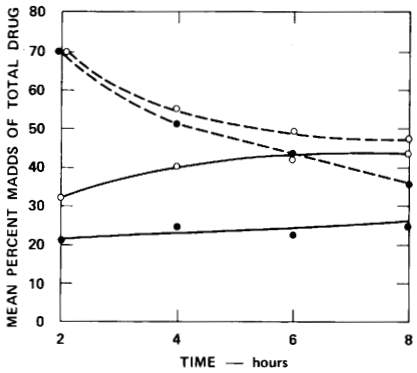

FIG. 1. Mean percentage MADDS of total drug at various times in the plasma of ♀ (○) and ♂ (●) Lewis rats receiving 1.0 mg DDS (—) or 1.2 mg MADDS (— —) per kg.

A similar comparison of sexes was not possible in Buffalo rats because no studies of male rats receiving MADDS were performed. However, female Buffalo rats exhibited the same approach to a steady state of acetylation–deacetylation at 8 hr after receiving either the low doses of the two drugs (57–67%) or the high doses (58–66%). That these ranges were higher in Buffalo rats than those found for female Lewis rats again suggests that the Buffalo strain was more capable of acetylating DDS.

The results from the plasma protein binding studies are summarized in Table III. The extent of binding of DDS and MADDS when mutually present in pooled plasma from animals receiving 5.0 mg DDS/kg (Study IV) or 5.8 mg MADDS/kg (Study VIII) was 67–72% for DDS and 91% for MADDS. When the individual drugs were studied separately by adding them to control plasma, the extent of binding was nearly the same as

TABLE III. BINDING OF DDS AND MADDS TO PLASMA PROTEINS OF ♀ BUFFALO RATS

Study	Drug level (μg/ml) DDS	Drug level (μg/ml) MADDS	Mean (± SE) percentage binding DDS	Mean (± SE) percentage binding MADDS
In vivo[a]	3.8[b]	2.0[b]	72 ± 1	91 ± 1
plasma	1.1[c]	6.2[c]	67 ± 3	91 ± 1
In vitro[d]	2.0	—	62 ± 1	—
plasma	—	2.0	—	81 ± 1
diluted	2.0	—	40 ± 2	—
plasma	—	2.0	—	64 ± 2

[a] Binding measurements were made in pooled plasma obtained 2, 4, 6, and 8 hr after the administration of either DDS or MADDS. Measurements were made in quadruplicate.

[b] Drug level in the pooled plasma sample from rats receiving 5.0 mg DDS/kg, intraperitoneally.

[c] Drug level in the pooled plasma sample from rats receiving 5.8 mg MADDS/kg, intraperitoneally.

[d] Binding measurements were made in undiluted plasma (6.2 g% protein) from untreated rats and in plasma diluted (1.0 g% protein) with 0.1 *M* phosphate buffer, pH 7.4. Drugs were added as indicated. Measurements were made in quadruplicate.

in plasma from animals dosed with either drug. Diluting the plasma to 1.0 g% protein reduced the binding of each drug but, in both cases, the percentage binding was still greater than one-half of the values obtained in undiluted plasma either *in vivo* or *in vitro*. The finding of nearly the same extent of binding *in vivo* and *in vitro* suggests that *in vivo* there was little or no competition by DDS and MADDS for available binding sites. This lack of competition was also indicated by the finding of nearly the same binding after DDS administration, in which the DDS level was approximately twofold greater than the level of MADDS, as after MADDS administration, in which the DDS level was one-sixth of the MADDS level.

Discussion. In contrast to mice (6), in which acetylation of DDS was barely detectable and deactylation of MADDS was rapid and nearly quantitative, we found that rats acetylated DDS readily and deacetylated MADDS incompletely. The apparent steady state of the two processes was found to be different in male and female Lewis rats. A similar phenomenon of acetylation–deacetylation was observed in our earlier studies of DDS and MADDS disposition in human subjects (7). However, different acetylation-deacetylation steady states in human subjects were not sex-linked, but related rather to their genetically determined capacities to acetylate DDS.

DADDS was not found to be a metabolite of either DDS or MADDS in the current studies. Thus, rats are similar to mice (6) and man (15) in being unable to acetylate both amino groups of DDS.

At the early time periods in these studies with rats, higher levels of MADDS were found after MADDS administration than after an equimolar dose of DDS. Such differences in levels of administered drug were also observed previously in rabbits (20), dogs (21), and human subjects (7). However, these differences were not found in two different strains of mice receiving equimolar doses of the two drugs (6). This finding in all species studied except the mouse probably results from the more extensive binding of MADDS than of DDS in the rat (Table III) as well as other species (17, 21), leading to limited distribution of MADDS to tissues and the maintenance of higher levels in the plasma compartment. Thus, the rat is more like man than the mouse in this regard.

No differences were found in the $T_{1/2}$ values for DDS in the sexes or strains of rats of the current work. They ranged from 5.0 to 6.8 hr, not greatly different from the $T_{1/2}$ of ^{14}C of 3–5 hr from the plasma of male Wistar rats receiving ring-labeled ^{14}C-DDS intravenously (22). The $T_{1/2}$ values using ^{14}C, it should be noted, represent a composite of the clearance of the parent drug and of all metabolites because only the radiolabel was measured. The $T_{1/2}$ values of DDS observed currently are slightly longer than the values of 2.4–3.4 hr found for mice (6), but are much shorter than the mean value of 29 hr found in various human populations (23). Also, the clearance rates of MADDS and DDS were the same in Buffalo rats but were significantly different in Lewis rats. In man, the clearance rates of the two compounds do not differ (23).

No data are available on the occurrence or levels of other metabolites in the plasma of

rats. In man receiving DDS, only DDS and MADDS have been found in the circulation by several laboratories (24–26). However, these compounds are minor urinary excretory products in both man and rats (7, 22, 27, 28).

It is apparent from the current studies that rats are better models of man than are mice in the disposition of DDS, but many differences exist that must be taken into account in the extrapolation of observations from rats to man.

The sex difference observed in the current study of Lewis and Buffalo rats, with female rats demonstrating higher capacities to acetylate DDS was confirmed in later studies of Lewis rats receiving dietary DDS (29). These results with DDS are in sharp contrast to reports of earlier studies with other arylamines. Thus, male Sprague–Dawley rats were found to acetylate more of an ip dose of sulfanilamide than did female rats (30). Likewise, male Wistar rats excreted a larger fraction of an oral dose of *p*-aminobenzoic acid as the *N*-acetylated metabolite than did female rats (31). However, these compounds are excreted primarily as the parent arylamines and their *N*-acetyl derivatives. As mentioned above, DDS and MADDS are minor excretory products of DDS in rats (22, 27, 28). The principal urinary metabolite of DDS is the mono-*N*-sulfate (27). Small amounts of *N*-glucuronides and *N*-oxidation products have also been reported (22, 27). The lower plasma levels of DDS and MADDS found in male rats in the current studies may be a reflection of their higher capacity to metabolize these compounds by pathways other than acetylation or deacetylation. It is well established that male rats exhibit greater abilities to metabolize such xenobiotics as hexobarbitone, amidopyrine, and antipyrine than do female rats (32, 33). Glucuronidation may be of particular importance because the glucuronyltransferase activity of liver from male rats has been shown to be greater than that of female rats (34).

Summary. Female Buffalo and Lewis rats receiving 1.0 mg DDS/kg ip exhibited higher plasma levels of DDS and its monoacetylated metabolite, MADDS, than did male rats of each strain receiving the same dose. The fraction of the total measured drug in plasma as MADDS at 8 hr in female rats of both strains ranged from 43 to 62% compared with a range of 28–31% in male rats. Plasma half times of disappearance ($T_{1/2}$) of DDS ranged from 5.0 to 6.8 hr and were not different among sexes and strains. Deacetylation of MADDS to DDS occurred when equimolar doses of MADDS were administered. An approach to a steady state of acetylation-deacetylation was indicated by comparing the percentage MADDS of the total drug in plasma in the respective sexes and strains receiving both drugs. $T_{1/2}$ values of MADDS were significantly lower than values for DDS in Lewis rats. They were not different in Buffalo rats. Protein binding studies in plasma from rats receiving 5.0 mg DDS or 5.8 mg MADDS/kg showed 67–72% binding of DDS and 91% binding of MADDS. These *in vivo* observations were confirmed by *in vitro* binding studies. Comparison of these results with those of earlier studies in mice and man indicates that the rat is a better model of man than is the mouse for studies on the disposition of DDS.

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