The pharmacokinetic parameters for MA are presented in the table below from the sponsor:

Table IVA: Individual and mean pharmacokinetic parameters of MODAFINIL acid in the dog after oral administration of a dose of 6.25 mg.kg^{-1} of MODAFINIL

Parameter	N	Mean	SEM	Median	Min	Max	C.V.
C_{max}	5	1.70	0.41	1.33	0.61	2.84	0.54
t_{max}	5	2.80	0.34	2.80	2.00	4.00	0.27
AUC_{0-12h}	5	11.70	2.55	12.43	2.55	17.57	0.49

Table IVB: Individual and mean pharmacokinetic parameters of MODAFINIL acid in the dog after oral administration of a dose of 12.5 mg.kg^{-1} of MODAFINIL

Parameter	N	Mean	SEM	Median	Min	Max	C.V.
C_{max}	5	3.83	1.02	2.29	2.07	6.88	0.60
t_{max}	5	3.10	0.62	2.50	2.00	5.50	0.48
AUC_{0-12h}	5	29.99	7.39	25.23	8.73	52.68	0.55

Table IVC: Individual and mean pharmacokinetic parameters of MODAFINIL acid in the dog after oral administration of a dose of 25 mg.kg^{-1} of MODAFINIL

Parameter	N	Mean	SEM	Median	Min	Max	C.V.
C_{max}	5	4.38	1.42	2.42	1.80	9.16	0.72
t_{max}	5	3.90	1.20	2.50	2.00	8.50	0.69
AUC_{0-12h}	5	38.72	10.01	34.39	14.31	73.33	0.62

Table IVD: Individual and mean pharmacokinetic parameters of MODAFINIL acid in the dog after oral administration of a dose of 50 mg.kg^{-1} of MODAFINIL

Parameter	N	Mean	SEM	Median	Min	Max	C.V.
C_{max}	5	6.05	0.99	6.18	3.22	8.79	0.37
t_{max}	5	3.00	0.45	3.00	2.00	4.00	0.34
AUC_{0-12h}	5	57.43	11.27	61.50	30.92	83.97	0.44

From these data, MA formation appears to be a nonsaturable process as evidant by the linear relationship between C_{max}, AUC, and dose. MDF clearance appears to be high (0.6L/hr/kg) and independent on dose, V_d is about 2 l/kg and also independent on dose.

Rabbits:
New Zealand white rabbits (5m) were injected single i.v. of 5mg/kg modafinil. Mean AUC_{0-inf} was 6ug.hr/ml anf terminal t1/2 was 1.2hr. Systemic plasma Cl was 1L/hr/kg which is slow compared to hepatic plasma flow of 2L/hr/kg. Apparent V_d was small 1.5L/kg. Modafinil acid elimination $t_{1/2}$ was similar to the parent with a mean of 1hr. Single oral doses of modafinil of 25, 50, 100mg/kg, were administered to 4m New Zealand white rabbits. Mean C_{max} were 2, 4, and 11ug/ml respectively and, the corresponding AUC_{0-inf} were 10, 30, 88ug.hr/ml. Linear relationship was seen between plasma level and dose and exposure and dose. Terminal $t_{1/2}$ ranged between 3-4hr. Modafinil acid was max conc and exposure incr with increasing the dose from 25-50mg/kg. However, at 100mg/kg, the values of modafinil acid were lower than those at 50mg/kg. This suggested that metabolism of modafinil to the acid maybe saturated at doses higher than 50mg/kg.

Repeate Dose:
Mice
Mice (both sexes) were treated twice daily with oral doses of 64mg/kg MDF for 4 days following 4 protocols. Group 1 given water for 5 days, group 2 dosed with water for 4 days and MDF on day 5 (day of investigation), group 3 dosed MDF for 4 days and water on day 5, and group 5 dosed MDF for all 5 days (repeate dosing). On day 5 mice were treated 30min prior to testing motility in actimeters; test lasted

30min. After end of study, mice were killed, blood and liver collected from each mouse and concentrations of MDF and its metabolite, MA, were determined by [redacted] Plasma concentration in the 4 groups are as follows:

	MDF	MA
gr 2	15±2	2.7±0.3
gr 3	0.2±0.06	0.02±0.01
gr 4	9±1	3±0.3

values are means±sem in µg/ml.

Results indicate that MDF plasma concentration after repeate dosing is lower than that after a single dose (gr 4 vs. gr 2), motor activity correlated best with plasma levels of MDF but not its acid metabolite, and MDF at high and repeated dosing induces its own metabolism as reflected by 20% increase in liver weight and decrease in MDF plasma level without change in MA concentration.

The above experiment was repeated for 18 days (investigation was conducted on day 19). MDF and MA plasma levels are as follows:

	MDF	MA
gr 2	16±1	3±0.2
gr 3	0.3±0.1	0.2±0.1
gr 4	7.2±0.6	2.5±0.4

values are means±sem in µg/ml.

Results are similar to those following 4 days of treatment.
It is concluded **that MDF produced linear dose-response, it induced its own metabolism as indicated by the enlarged liver and decrease in MDF concentration after repeate dosing without changes in MA levels.**

Dog

Six dogs were orally dosed 30mg/kg of MDF for 15 days. On days 1, 8, and 15 each dog received both a 30mg/kg antipyrine (enzyme inducer) and 30mg/kg MDF. Blood samples were collected at specified times up to 24hr postdose and drug levels determined by [redacted] analysis.

Antipyrine kinetic parameters:

Days:	1	8	15
$t_{1/2el}$ (hr)	1.84±0.32	0.73±0.05	1.1±0.2
$t_{1/2abs}$ (hr)	0.36±0.14	0.52±0.09	0.4±0.1
AUC_{exp} (ug.hr/ml)	108.47±13	49.1±2.42	47.34±4.4
C_{max} (ug/ml)	29.68±2.11	23.44±1.43	19.1±1.7
T_{max} (hr)	1.42±0.27	1±0.13	1.33±0.2

Administration of MDF increased total clearance of antipyrine with time (0.3 day1 to 0.7 l/hr/kg day15), decreased C_{max}, AUC_{exp}, and $t_{1/2el}$, and slightly caused an increase in $t_{1/2abs}$ but no effect on T_{max}. Most of the siginificant effects occurred between day 1 and 8 and no apparent differences were noted between days 8 and 15.

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Tables below present the kinetic parameters for modafinil and modafinil acid:

Table VIA: Repeated doses of MODAFINIL in the dog: pharmacokinetic parameters of MODAFINIL acid after MODAFINIL on Day 1

Parameters	N	Mean	SEM	Median	Min	Max
C_{max}	6	6.27	0.98	6.75	2.77	9.23
t_{max}	6	3.67	0.83	3.50	2.50	6.00
AUC_{0-24h}	6	60.70	11.69	60.99	21.06	101.12
C_{min}	6	0.00	0.00	0.00	0.00	0.00

Table VIB: Repeated doses of MODAFINIL in the dog: pharmacokinetic parameters of MODAFINIL acid after MODAFINIL on D8

Parameters	N	Mean	SEM	Median	Min	Max
C_{max}	6	4.99	0.75	5.23	2.34	7.83
t_{max}	6	3.83	0.25	3.75	3.00	4.50
AUC_{0-24h}	6	48.12	9.68	44.61	18.70	86.92
C_{min}	6	0.16	0.16	0.00	0.00	0.94

Table VIC: Repeated doses of MODAFINIL in the dog: pharmacokinetic parameters of MODAFINIL acid after MODAFINIL on D15

Parameters	N	Mean	SEM	Median	Min	Max
C_{max}	6	6.56	0.64	6.05	4.69	8.61
t_{max}	6	3.08	0.15	3.00	2.50	3.50
AUC_{0-24h}	6	43.79	9.25	43.60	13.69	78.19
C_{min}	6	0.10	0.07	0.00	0.00	0.38

Table [illegible]: [illegible] pharmacokinetic parameters of MODAFINIL on Day 1

Parameters	N	Mean	SEM	Median	Min	Max
C_{max}	6	14.88	2.02	16.27	5.61	18.84
t_{max}	6	3.25	0.67	3.00	1.50	6.00
AUC_{0-24h}	6	150.48	17.71	159.68	65.73	182.96

Table IVB: Repeated administration of MODAFINIL in the dog: pharmacokinetic parameters of MODAFINIL on Day 8

Parameters	N	Mean	SEM	Median	Min	Max
C_{max}	6	7.50	0.60	7.48	5.28	9.24
t_{max}	6	2.83	0.38	2.50	2.00	4.00
AUC_{0-24h}	6	59.87	9.64	53.72	31.87	91.09
C_{min}	6	0.29	0.13	0.26	0.00	0.72

Table IVC: Repeated administration of MODAFINIL in the dog: pharmacokinetic parameters of MODAFINIL on D15

Parameters	N	Mean	SEM	Median	Min	Max
C_{max}	6	8.05	0.80	7.58	5.64	11.22
t_{max}	6	3.17	0.36	3.25	2.00	4.50
AUC_{0-24h}	6	47.71	7.82	48.21	23.36	74.69
C_{min}	6	0.41	0.25	0.18	0.00	1.64

MDF caused a significant decrease in C_{max} and AUC without an effect on T_{max} or C_{min}. These results show that modafinil changed its own kinetics and that of antipyrine through enzyme induction. In comparison to MDF, the kinetics of MA were not changed by repeated dosing of modafinil (Table above).

The effects of phenobarb as an enz inducer, on disposition of modafinil was tested using antipyrine as an enz inducer control. Five male beagle dogs recieved phenobarb orally between days 2-14 and each

recieved 30mg/kg p.o. modafinil and 30mg/kg p.o. antipyrine on days 1, 8, and 15. Max conc of modafinil were 9ug/ml d1, 5ug/ml d8, and 4ug/ml d15, the corresponding AUC_{0-inf} (d1 and $AUC_{0-\tau}$ on d8&24) values were 72, 22, and 14ug.hr/ml respectively. Both max conc and exposure were lower on days 8&15 from those on d1. The $AUC_{0-\tau}$ for antipyrine, induction control, on d8 & 15 were 42&24ug.hr/ml respectively. It was concluded that phenobarb alters PK parameters of modafinil as it did for antipyrine.

DISTRIBUTION AND ELIMINATION

Rat

^{14}C-labeled MDF was used in all distribution, metabolism, and excretion studies with specific activity of 200µCi/mg and 97-98% puritiy. Male and female Sprague-Dawley rats were administered 5mg/kg cold MDF i.v. and 50 and/or 100mg/kg orally. Drugs prepared in 5% gum arabic oral suspension or in 1% ethanol solution. Follwoing single i.v. administration, MDF was rapidly distributed and radioactivity was detected within 3min after injection with $t_{1/2}$ of 2hr in males and 4hr in females, C_{max} 2 (expressed as a value of F) in both sexes, and AUC in males was 5 and in females 8. It was concluded that there is **no sex differences in plasma concentration, $t_{1/2}$ is shorter in males vs. females, and elimination followed 2-compartment model.**

Following oral dosing, MDF was rapidly absorbed with radioactivity detected by 10min postdose, no sex differences except for slightly higher plasma levels in females than in males, $t_{1/2}$ in males was shorter, 5hr, than in females, 9hr, and absolute bioavailability in males was 89% and, 85% in females.

Following oral administration, MDF was widely distributed to tissues with high levels measured at 0.25hr postdose in liver, jejunum, kidney, and thyroid and by 24hr radioactivity was very much reduced in all tissues. At 96hr in male and female rats, radioactivity level was highest in fur, this was proposed by the sponsor to be caused by urine contamination. Results were similar in males and females except for higher radioactivity in ovaries than testes. It seems that the drug does not accumulate over time. Brain levels were small but constant throughout the selected measurements.

Following repeated oral administration of 100mg/kg for 8 days, MDF seemed to accumulate (attached Table) and elimination was slower after repeate dose by a factor of about 2, than after single administration.

It is concluded **that after single oral dose of [redacted]C-modafinil to the rat, absorption was rapid and plasma levels were the same in both sexes. Elimination $t_{1/2}$ however, was longer in females than in males (9 vs. 5hr respectively). Similar results recorded after i.v. with $t_{1/2}$ of 2 and 4hr in males and females respectively. Drug was distributed rapidly to many tissues and elimination was mainly by urine. Fecal elimination was higher after oral dosing (20-30%) than after i.v. (7-8%). Substantial biliary elimination was noted (17-32%) indicating enterohepatic circuling of the drug. Elimination following repeate dosing was slow indicating the drug's tendency to accumulate.**

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Table XXVII: Elimination half-lives of the radioactivity after single and repeated doses of MODAFINIL in the rat

Organ	males		females	
	SD	RD	SD	RD
Liver	20.9	24.5	25.4	29.3
Heart	26.6	7.1	26.7	51.3
Kidney	21.9	30.4	21.8	37.9
Brain	26.4	44.4	24.6	52.5
Spleen	26.0	40.1	24.7	49.4
Pancreas	24.2	32.4	21.8	46.9
Lung	25.2	42.5	25.6	60.4
Testis/ovary	28.7	41.7	24.9	46.5
Lumbar musc.	26.3	67.4	21.0	57.1
Paw musc.	25.5	51.8	20.8	96.0
Fur	15.6	34.1	64.8	63.6
Bones	29.3	2257.6	32.8	290.0
Intestine	19.7	24.0	16.0	21.9
Hypophysis	173.5	58.9	35.3	46.1
Thyroid	30.9	31.1	23.9	41.7
Adrenal	27.5	47.4	34.1	59.4
Eye	23.7	41.9	20.5	79.8
Fat	41.8	65.2	36.2	624.3
Skin	30.0	62.1	27.4	66.9
Plasma	17.9	21.4	17.7	27.5

Table XXVIII: Distribution of radioactivity in the rat in descending order of F values (single dose/repeated dose)

Time	1 h				24 h				96 h			
Administration	SD		RD		SD		RD		SD		RD	
Sex	Males		Females		Males		Females		Males		Females	
Plasma	4	9	4	8	18	16	14	15	18	20	16	20
Liver	1	1	2	2	1	7	3	2	4	1	2	10
Kidney	2	2	1	3	5	6	4	5	5	6	5	5
Heart	11	12	12	11	11	11	16	13	9	15	13	21
Brain	18	20	17	20	13	20	10	20	18	19	16	23
Spleen	9	10	11	14	16	11	9	6	11	13	11	14
Pancreas	7	3	5	9	9	9	6	11	8	9	7	12
Lungs	8	11	9	9	6	10	8	6	8	12	7	7
Jejunum	3	8	1	1	3	3	2	7	12	17	14	18
Testis or ovaries	17	18	7	20	6	15	10	12	13	16	7	13
Lumbar muscle	14	17	8	15	13	17	16	17	15	11	18	17
Paw muscle	12	16	13	17	13	18	12	16	16	16	15	9
Fur	15	5	15	6	4	1	5	3	3	3	3	3
Skin	10	13	9	12	10	8	16	9	7	5	7	6
Bones	13	14	16	16	12	11	19	12	12	7	11	2
Fat	-	7	18	19	14	5	20	19	17	3	14	4
Thyroid	6	4	-	5	3	3	3	4	3	7	6	8
Hypophysis	12	5	15	13	20	14	15	18	2	20	6	15
Adrenals	5	6	6	6	4	4	7	3	6	4	3	3
Eye	16	19	14	18	18	19	12	12	18	18	20	14

Modafinil is eliminated mainly by urine and some in feces. Following 50mg/kg i.g. dose, total elimination of radioactivity at 24hr postdose was 80% (54% in urine and 26% in feces) in males and 69% in females (59% in urine and 10% in feces). These values increased to 87 and 77% in males and females respectively by 96hr. Similar elimination percent noted after 5mg/kg i.v. or 100mg/kg i.g. dose. The absolute bioavailability of radioactivity was 79 and 84% in males after 50 and 100mg/kg and 89 and 92% in females at the same doses.

Following gastric or i.v. administration, bile was collected over 24hr. Data showed that MDF entered the enterohepatic circulation. Biliary elimination was fast and higher in females than in males (23 and 11% at 2 hr and 36 and 21% at 24hr respectively). Bioavailability factor calculated on the basis of biliary elimination was 85%. In bile cannulated SD rats (3/sex/route) [redacted]C-modafinil was administered either i.v. at 5mg/kg or orally at 100mg/kg, sampling done over 24hr. Biliary excretion was generally higher in f than m. Two hours after oral dose, bile of m&f contained 8 & 17% of radioactive dose respectively. Cummulative amount of radioactivity in bile 24hr postdose was 18&33% of dose respectively. Total 24hr urinary elimination accounted for 40% of dose in either sex. Amount of radioactivity excreted in 24hr bile after i.v. dose of 5mg/kg was similar to theat after p.o. dosing with 21&36% in m&f respectively. Urinary elimination after i.v. was higher than that after p.o. ranging between 50-60% of administered dose. Comparison of fecal and biliary elimination suggested enterohepatic recycling.

Dog

Tables below present PK parameters and tissue distribution of oral 30mg/kg cold dose of MDF and 10uCi/kg in dogs. Elimination $t_{1/2}$ was 3hr, C_{max}, T_{max}, and V_d varied between animals. Distribution was rapid and high levels of radioactivity were detected in the 2hr samples.

Distribution was similar to that in the rat, but higher levels were found in the dog brain (distribution was homogeneous throughout the different regions). By 24hr, radioactivity was significantly decreased in all tissues. Elimination seems to be slower in the dog than in the rat. **About 72% of radioactivity was eliminated within 72hr by urine (65%) and feces (9% of administered dose).**

Table [illegible]: Radioactive concentrations in the tissues expressed in descending order of P values

Tissue	Dog 64	Dog 61
	2 h	24 h
Plasma	2	8
Liver	4	2
Kidney	1	1
Heart - atrium	12	9
Heart - ventricle	13	11
Brain:		
Frontal cortex	10	14
White matter	11	17
Grey matter	7	14
Striatum	9	13
Cerebellum	8	14
Spleen	19	23
Pancreas	3	6
Lung	14	25
Jejunum	25	3
Testi	6	8
Lumbar muscle	16	20
Fav muscle	17	21
Skin	21	10
Fur	5	4
Fat - pericardial	24	21
- perirenal	28	24
Thyroid	20	9
Hypophysis	23	15
Adrenal	18	7
Eye	22	

Table [illegible]: Pharmacokinetic parameters of [illegible]C)-MODAFINIL after oral administration in the dog of 30 mg.kg^{-1} and 10 µCi.kg^{-1}

Parameters	61 P1	61 P2	70 P1	70 P2	C2F64 P1	C2F64 P2	Mean	SEM
T1/2el	2,26	2,03	4,64	4,60	4,79	1,73	3,34	0,60
T1/2abs	0,93	1,07	2,83	2,92	0,55	1,31	1,60	0,42
Lag_t	0,61	0,00	1,06	0,91	0,61	0,23	0,57	0,16
AUC_exp	4,11	6,89	16,25	14,41	5,27	5,40	8,72	2,13
Cmax	0,86	0,88	1,13	1,20	0,57	0,87	0,89	0,10
Tmax	1,50	1,00	7,00	6,00	2,50	2,00	3,33	1,03
Cirtot	2,43	1,46	0,62	0,69	1,90	1,85	1,49	0,29
Vd	7,95	4,24	4,12	4,61	13,10	4,63	6,44	1,46
MRT_exp	5,17	5,83	8,35	7,72	8,61	5,65	6,89	0,62
Vdss_ex	12,57	8,45	6,14	6,36	16,33	10,46	9,72	1,77
AUC_mod	4,12	5,22	15,98	15,74	5,10	5,25	8,57	2,31
MRT_mod	5,21	4,14	11,83	11,77	8,31	4,62	7,65	1,44
Vds_mod	12,65	7,93	7,40	7,47	16,31	8,79	10,09	1,48

Below is a summary table for elimination of modafinil in various species including humans.

Table 2.5-12. Urinary/Fecal Excretion Patterns in Preclinical Species and Man

Percent of Radioactive Dose recovered from Urine or Feces							
		Rat					
	Mouse	Sprague-Dawley	Long-Evans	Guinea Pig	Rabbit	Dog	Man
Urine	69	63-93	73	62	60	64	80
Feces	21	5-16	7	4	6	9	1

METABOLISM

Investigated in the rat, mouse, dog, and rabbit. The sponsor indicated that because MDF is heat sensitive, [redacted] could not be used for analysis, therefore, MDF labelled at [redacted]C- (in the acetamide chain) and ^{3}H- (in the aromatic ring) were used. Synthesis and purity data were provided and are acceptable.

Sprague-Dawley and NMRI male mice were injected i.p. with a mixture of cold MDF (100mg/kg) and one of the two labeled MDF (100µCi/kg). Urine was collected over 24hr and acidic and non-acidic metabolites were extracted and quantified using [redacted] Fractions extracted from the non-acid medium were similar regardless of the label administered (32 and 21% of total eliminated radioactivity for ^{3}H- and [redacted]C- respectively). However, the fractions for the acid metabolites differed depending on the label used with 54% for the ^{3}H- and 18% for the [redacted]C-label. The non-extractable portion paralleled the ^{3}H-label accounting for 15% of total radioactivity but after administration of the [redacted]C-label this fraction accounted for 60% of total activity. These differences seem to suggest that metabolism depends on the isotope used. However, the sponsor indicated that since cold MDF was used simultaneously with the label, therefore, the label served only as the tracer and unlikely will account for the large differences observed. These differences suggest the metabolism of MDF involves formation of 2 molecules with cleavage perhaps at the sulfur atom. The proposed molecules are: thioglycolic acid or acetic acid (nonsulfur), thioacetamide or acetamide or, S-oxide derivatives.

Modafinil was extracted from the non-acid fraction (30% in rat and 50% in mouse) and no S-oxide derivatives were found. In the acid fraction the majority of radioactivity (50%) was identified as modafinil acid (MA) in both species. Using in vitro microsome preparation, modafinil sulfone derivative which corresponds to the S-oxide was identified. This metabolite was also identified in plasma from rats treated with high doses of modafinil.

It is concluded that **modafinil is the main compound in the non-acid fraction and MA is the main metabolite in the acid fraction. Modafinil acid is also identified and quantified in plasma from animal and human PK studies. Also found but not identified, are smaller compounds formed by cleavage at the sulfur atom. Modafinil sulfone identified in phenobarbitone-induced rat microsomes is also detected in in vivo studies in rats administered high doses of modafinil.**

Urinary and fecal metabolic profile of modafinil was studied in NMRI mice, SD & Long Evans rats, Dunkin-Hartley g. Pigs, and New-Zealand rabbits following 100mg/kg p.o dose and 5mg/kg i.v. (4m/species/strain/route). The metabolic profile was qualitatively similar in all species with the major fraction of urinary activity represented small molecules resulted from cleavage of the 2-carbon ^{14}C-fragment of modafinil side chain. In the rat, this fraction represented >90% of urinary activity over 24hr period. Modafinil acid was the main product representing 11% in mice, 5% in rats, >40% in rabbits, and 36% in g.pigs. Guinea pigs were the only species where the sulfone and sulfide were the main metabolites (27% sulfone). Modafinil and its metabolites were determined in CD-1 mice, SD rats, and beagle dogs following 30mg/kg p.o. (30uCi/kg of [redacted]C-modafinil). In mice, LC/MS analysis of 24-hr urine samples showed presence of modafinil, modafinil acid, and 3 glucuronides of ring hydroxylated products, each representing <10% of total radioactivity. Mean conc of modafinil, modafinil acid, and sulfone in the 24-hr urine following single dose were 19, 18, and 4ug/ml respectively, and those following repeate dosing were 15, 16, and 3ug/ml respectively. Conc of modafinil or its metabolites could not be detected in plasma of mice 24hr postdose. In rats, the main urinary metabolite was the acid at 70% with small amounts of modafinil, modafinil acid sulfone and glucuronide conjugates of hydroxy modafinil each about 4-10% of adninistered dose. Rat urine at 0-4, 4-12, and 12-24hr periods contained modafinil acid at 75, 23, and 7ug/ml respectively, the sulfone levels were below quantitation limit, and modafinil level at 0-4hr was 9ug/ml and at 4-12hr was 2ug/ml. Following multiple dosing in the rat, modafinil urinary levels were 8, 4ug/ml and, below quantitation limit at the 3 collection periods and the corresponding values for modafinil acid were 37, 33, and 12ug/ml respectively. Similar to the mouse, rat plasma levels of modafinil or its metabolites could not be detected at 4, 12, or 24hr after single or repeate dosing. In dogs, the acid metabolite was the main urinary metabolite at 46-69% of dose at 0-4hr, with modafinil at 6-13%, and one

glucuronide at 1-7%, and 11-31% of solvent front radioactivity. Modafinil mean urinary conc after single dose were 66, 53, and 6ug/ml at 0-4, 4-12, and 12-24hr periods, and those for the sulfone were 4, 16, and 9ug/ml respecetively. Following multiple dosing, modafinil urinary levels in the 3 periods were 50, 4, and 0.7ug/ml respectively; those for the acid were 304, 90, and 19ug/ml respectively, and those for the sulfone were 13, 8, and 3ug/ml respectively. Mean modafinil plasma levels at 4, 12, and 24hr post single dose were 9, 1ug/ml, and below quantitation limit, the corresponding conc for the acid were 6, 0.5ug/ml, and below quantitation limit, and those for the sulfone were 3, 1ug/ml and below quantitation limit respectively. Following repeate dosing, levels detected only after 4hr at 2, 3, and 2ug/ml for modafinil, acid, and sulfone respectively.

Spregue-Dawley (3m) and New-Zealand rabbits (3m), were orally dosed 100mg/kg modafinil. GC-MS analysis of urinary samples identified benzhydrol, OH-benzhydrol, Dihydroxy-benzhydrol, hydroxyphenylmethane, and dihydroxydiphenylmethane, which are products of side-chain cleavage of modafinil. In a separate study in SD rats, there was no evidence of production of modafinil sulfide or acid sulfide in rat plasma 30min or 4hr post 128mg/kg i.p. of modafinil.

In vitro studies using rat, dog, and human hepatocytes were done. The racemate and each of the stereoisomers were tested. There was no chiral inversion of modafinil enantiomers and the l-isomer seemed to be more extensively metabolized than the d-isomer which is opposite to that seen in in vivo. However, only 1% of modafinil was converted to the acid in this study. Six metabolites were found (most not identified) in human hepatocytes by [redacted] The sulfone was 1-2% of total radioactivity, the acid 25% of total radioactivity at the lowest conc but only 3% at the highest, all remaining radioactivity was unchanged modafinil (75-94%). The sponsor in this study concluded that there was no evidence for autoinduction of modafinil following pre-incubation with cold drug, nor for formation of glucuronide or sulfate conjugates. Another study investigated auto-induction in human hepatocytes using liver samples from 3 volunteers and standard inducers. Exposure to modafinil for 72hr incr activities of most CYPs about 1.5-4x vs. the negative controls. These incr occurred at the highest conc of 1mM of modafinil. Using human microsomes, it was shown that CYP3A4 is the isozyme responsible for the formation of the sulfone and that formation of the acid does not seem to involve a cytochrome P450-mediated metabolism.

Table 2.5-11. Species Comparison of Urinary Elimination of Individual Metabolites

Approximate Percent of Urinary Excretion Fraction[a]							
Metabolite	Mouse	Rat (Sprague-Dawley)	Guinea Pig	Rabbit	Dog	Man	
						0-4 hr	4-12 hr
Solvent Front [b]	58-68	83-90	14	43	11	3	18
Modafinil	9-12	-[c]	4	2	12	8	7
Modafinil Acid	10-12	4-5	29	44	69	76	52
Modafinil Sulfone	1	-	1	-	-	-	-
Ring-Hydroxylated Modafinil [d]	5-22	-	-	8	1	7	13
Ring-Hydroxylated Modafinil Acid	-	-	-	-	-	6	5
Modafinil Acid Sulfone	-	-	34	3	-	-	4
Modafinil Sulfide	-	-	16	-	-	-	-
Reference	DM-96-048 DM-96-007		DM-96-048		DM-96-007	DM-96-029	

[a] The figures represent the percent of the total urinary modafinil and metabolites found in urine as determined following single oral dosing with radiochain-[^{14}C]-modafinil only.
[b] Solvent front represents the summation of material which appears at the solvent front of chromatograms. This peak is thought to represent the small-molecule products of modafinil side-chain cleavage.
[c] Compound was not detected or was found at less than 1% in the urine.
[d] Percentages presented for ring hydroxylated metabolites is the summation of all ring hydroxylated enantiomers and their glucuronides.

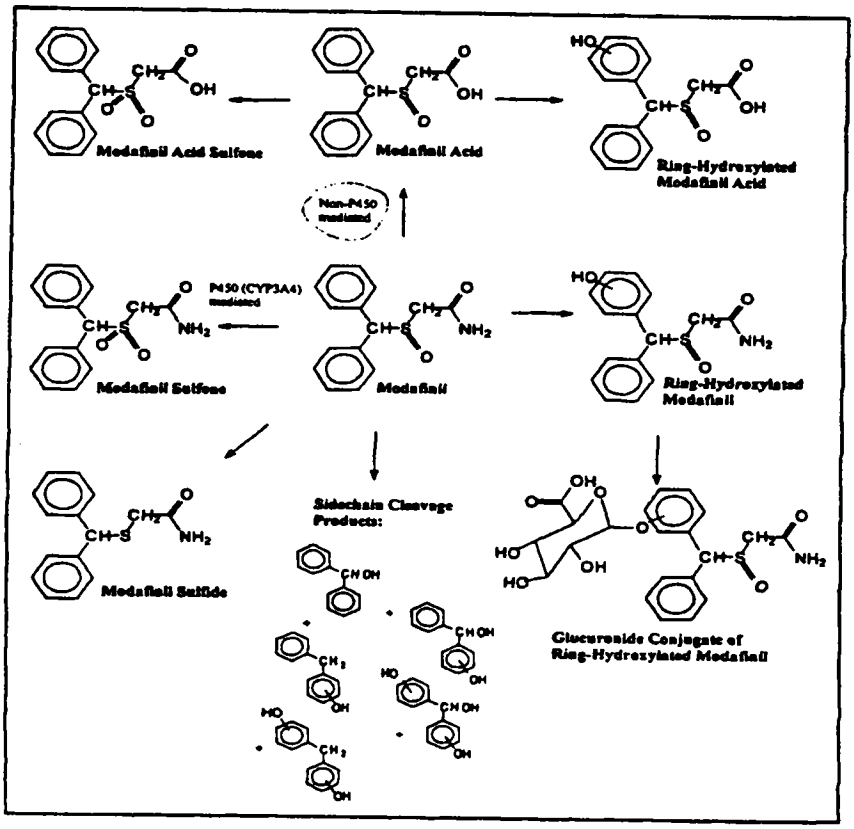

Figure 2.5-2. Metabolic Pathways of Modafinil.

PK of the Stereoisomers, d & l:

stereospecificity played a role in modafinil absorption and metabolism.

Mouse/i.p. of 64 mg/kg:

1. MDF and its isomers were absorbed,
2. MDF and its acid metabolite appeared in plasma,
3. MDF plasma concentration was very high (30µg/ml) compared with 10µg/ml in dog dosed 30mg/kg and 4µg/ml in rat orally dosed 256 mg/kg.
4. plasma concentration of l-isomer were higher (50-60 µg/ml), than those of MDF ≈25 µg/ml. Whereas those of the d-isomer were comparable to those of MDF. $AUC_{0.25\text{-}2hr}$ after MDF was 36 and increased to 64 mg.hr/l after the l-isomer.
4. $t_{1/2}$ of MDF was short 1.2 hr
5. concentrations of d-isomer acid were higher than those of l-isomer and MDF acid whereas, concentration of l-isomer acid and MDF acid were comparable.

Dog/30mg/kg oral-crossover design:

Compound	C_{max}	t_{max}	$t_{1/2e}$	Cl_{tot}
MDF	10±2.5	2±0.4	3±1	0.5±0.2
levo	16±2.6	2.5±0.4	4±1	0.23±0.05
dextro	12±2.7	2±0.4	3±0.6	0.5±0.1

Compound	C_{max}	t_{max}	$AUC_{0\text{-}24hr}$
MDF acid	6±1	3±0.1	52±12
levo-acid	2±0.1	3±0.4	17±3
dextro-acid	19±6	3±0.4	126±36

values are means±sem

$AUC_{0\text{-}24h}$ in mg.hr/l, C_{max} µg/ml, time in hr

C_{max}, $AUC_{0\text{-}24h}$, as well as total clearance are significantly different between l-isomer and MDF. Value of $AUC_{0\text{-}24h}$ after l-isomer was double (147 mghr/l) that of MDF or d-isomer (≈72 mg/l.hr), but total clearance was lower in l-isomer than that of MDF or d-isomer. The acid metabolites were also significantly different specifically those of the d-isomer as noted above.

Conclusion: The isomers exhibited different kinetics. The d-isomer seems to be more readily and completely absorbed than the l-isomer or MDF and the l-isomer is less readily metabolized to the acid than either the d-isomer or MDF. C_{max}, $AUC_{0\text{-}24}$, and total clearance of MDF were similar to those of the d-isomer but different between the l-isomer and MDF. Significant differences noted in $C_{max\text{-}acid}$ and AUC_{acid} after the d-isomer or MDF but no differences after the l-isomer.

Kinetics of MDF-acid in the dog:

Doses: 75, 150, 300, 600 mg/kg orally in a cachet.

MDF-acid administration:

- slow absorption (t_{max} 2.4 hr) and dose-independent
- no relationship between dose and clearance (2-4 mg/l.hr) and was higher than that of MDF. **Check**
- V_d increased proportionally to dose
- C_{max} (7, 10, 13, 18 µg/ml), and AUC increased linearly with dose (33, 48, 102, 162mg.hr/ml respectively).
- $t_{1/2}$ ranged between 2-6hr.

Kinetics of MDF-acid in the SD rat:

Male SD rats were fitted with a straight intraventricular catheter to allow multiple blood sampling. SKF 525A (enzyme inhibitor) was administered i.p. at 75mg/kg; the control group was administered physiological saline under the same conditions. Modafinil was administered i.p. at 64, 256, or 512mg/kg 3hr post SKF. In the absence of SKF, the $AUC_{0.25\text{-}24hr}$ for MA was >2 fold of the parent drug and the increase was not proportional to dose. Following SKF, modafinil AUC was markedly increased over that without SKF but AUC for MA was lower than that for MDF (Tables below). The results indicate that

pretreatment with SKF 525A modify the kinetics of MDF and its metabolite as reflected by the increased concentrations, this increase was inversely proportional to the dose: the higher the dose the lower the increase.

It is concluded that the drug is absorbed, the increase in AUC is not proportional to dose and the kinetics is not linear. The marked increase in AUC of MDF after pretreatment with SKF 525A is indicative of the enzyme inducing ability of the drug.

Table I: [illegible] in mg.l^{-1}.h of MODAFINIL and of MODAFINIL acid in the control rat

Dose of MODAFINIL (mg.kg^{-1})	64		256		512	
	mean	SEM	mean	SEM	mean	SEM
MODAFINIL	2.17	0.36	3.66	0.25	35.62	6.84
MODAFINIL acid	5.38	0.68	10.32	2.88	51.64	6.68
Metab./MODAFINIL ratio	2.58	0.31	2.75	0.62	1.54	0.22

Table II: $AUC_{0,24-4h}$ in mg.l^{-1}.h of MODAFINIL and of MODAFINIL acid in rats pretreated with SKF 525A

Dose of MODAFINIL (mg.kg^{-1})	64		256		512	
	mean	SEM	mean	SEM	mean	SEM
MODAFINIL	71.09	18.36	216.84	37.41	229.51	68.12
MODAFINIL acid	52.14	7.86	99.39	13.10	104.39	22.90
Metab./MODAFINIL ratio	0.78	0.07	0.49	0.10	0.56	0.12

The PK of modafinil acid (64 or 256mg/kg i.p.) was studied in rats with or without 75mg/kg SKF 525. There was no sig difference in plasma levels of modafinil acid in presence or absence of SKF. This indicated that metabolism of modafinil acid does not involve P450.

Special PK Studies

Exposure of bone marrow to modafinil was studied to confirm exposure in the micronucleus in vivo cytogenetic assay. [redacted]C-Modafinil at 0.5 and 5mg/kg (100&1000uCi) was administered orally to OF-1 mice on consecutive days. Radioactivity in bone marrow was much higher than background 24hr after the 2 doses of modafinil compared with the cont. Bone marrow exposure was relatively proportional to dose and there was no sex difference in exposure at either dose.

Autoradiography of [redacted]C-modafinil was done in pregnant SD rats. Pregnant females were orally dosed modafinil at 100mg/kg orally on gd17 and killed at 1, 8, 24, and 72 hr postdose. At 1hr, highest radioactivity was seen in liver, kidneys, blood vessel walls, heart, and Harderian gland. Lower radioactivity was detected in the brain and spinal cord. Some radiolabel was detected in all other tissues. Radioactivity was comparable in fetus and placenta to other maternal tissues. At 8hr radiolabel was decr but distribution pattern was the same. Levels were further decr by 24 and 72hr but remained detectable in Harderian gland, brown fat, and fecal pellets. [redacted]C-modafinil was detectable in milk 1hr after dosing of 100mg/kg to lactating female SD rats at 24ugEquiv/g and peak radioactivity in plasma occurred at 0.5hr postdose at 28ugEquiv/g. By 24hr postdose, radioactivity was nearly gone from plasma but milk conc were 29-75% of the peak value.

TOXICOLOGY:

ACUTE TOXICITY:
LD_{50} values in the rat/oral: 1640±109 mg/kg, mice/oral: 1370±93 mg/kg, dog/oral: a dose of 400 mg/kg caused 2/3 deaths 28 and 72 hr postdose.

In general, clinical signs in mice and rats included: hyperkinesia, stereotypy, loss of balance, convulsions, ptosis, dyspnea, hypersensitivity to noise (rat), and exophthalmus (rat). In the dog, symptoms included: weight loss, hyperactivity, stereotypy, mydriasis followed by miosis, localized opacification of cornea, reddening of face, eye lid, and conjunctiva, and tachycardia with tachypnea at high doses (>300 mg/kg).

Gross necropsy was normal in mice and rats dosed orally. Animals dosed by i.p. route showed MDF deposition on liver (mice) or pale discoloration of kidneys and deposition on liver in rats. In the dog, blood was noted in urinary tract of 2/3 200 mg/kg and 1/3 dogs dosed 400 mg/kg.

SUBCHRONIC TOXICITY:

- 13-week oral dietary study in OF-1 mice (GLP)
- 13-week oral dietary study in OF-1 and CD-1 mice (GLP)
- 4-week oral study in rat (Non GLP)
- 12-week oral study in rat with 4 wk recovery period (Non-GLP)
- 13-week oral dietary study in rats (GLP)
- 12-week oral study in dog (Non GLP)

Mouse:
- 13-week mice/GLP/DS-93-005/1988: OF1 male and female mice (70/sex/dose) administered MDF in the diet at the following doses: 25, 75, 100, 150 mg/kg/d for 13 wk.
- No drug-related deaths.
- Non-dose dependent changes in: Hb decr 4.5% in f dosed 25mg/kg, 8% in f dosed 100mg/kg, and 5% in f dosed 150mg/kg. Bilirubin decr (except at 75mg/kg no change) in m dosed 25mg/kg (19%), in males dosed 100mg/kg (16%), and m&f dosed 150mg/kg 16&28% respectively). Reticulocyte no. incr in f dosed ≥75mg/kg. Cholesterol decr 23% in f & 25% in m dosed 100&150mg/kg.
- Dose-dependent incr in liver wt both sexes (m: 7, 15, 25, 39% of cont; f: 8,22,27,35% of cont in 25, 75, 100, and 150mg/kg doses respectively).

A NOEL could not be determined because of some finding noted in each dose gr. TK was not done in this study.

Comment: doses in this were selected based on a pilot study (H-IFT No.605406/not provided) which showed 100 mg/kg dose caused a decrease in growth rate of males. Mean actual doses administered was based on mean food consumed/wk and mean body weight determined in the middle of the wk: there seem to be an agreement between calculated and actual doses with maximum variation of no more than 20%.

- 3mo oral dietary study in CD-1 mice/DS-95-002/Hazleton VA/Initiation date: Mar 14 1995/GLP.
Species/Strain/age/wt at initiation: CD-1 mice/6wks old/24-29g m and 19-23g f.
Doses*/no. per dose: 0, 60, 120, and 180mg/kg/d/10/sex/dose.
Route/Duration: dietary admixture/3mo.

* doses were selected as multiples of the HD (60mg/kg/d) used previously in the 18mo carcinogenicity study.

Parameters assessed: mortality and clinical signs (2x daily), B.wt & Food inatake (pre dose and weekly), Hematology & clinical chem (via orbital sinus; day 87 & 93 respectively, from *fasted* mice), organ wts, gross exam, and histopath (only lung, liver, kidneys, heart, and any gross lesions from all mice). A TK study (DS-95-003) was also conducted.

Results: [table below from sponsor]

Table 1. Subchronic toxicity study to establish the MTD of modafinil in CD®-1 mice (DS-95-002)[a] : Incidence or Mean (± S.D.) Values

		Modafinil Dose (mg/kg/day in food)			
		0 (Control)	60 (Low-Dose)	120 (Mid-Dose)	180 (High Dose)
Body Wt Change (g)	M	10.3 ± 1.7	8.5 ± 1.7	8.5 ± 2.0	6.4 ± 1.4
	F	8.2 ± 2.3	7.4 ± 1.3	7.9 ± 2.4	7.8 ± 1.2
Rough Haircoat	M	3/10	3/10	5/10	6/10
	F	0/10	2/10	1/10	0/10
Urogenital Staining	M	0/10	2/10	4/10	4/10
	F	0/10	0/10	0/10	0/10
Hematocrit (%)	M	46.0 ± 1.6	46.3 ± 0.7	46.8 ± 3.2	43.6* ± 0.2
	F	47.3 ± 1.8	46.2 ± 3.0	49.2 ± 2.9	46.8 ± 3.2
Liver Wt.:fasted (g)	M	1.30 ± 0.1	1.36 ± 0.1	1.46 ± 0.2	1.64* ± 0.1
	F	1.23 ± 0.2	1.12 ± 0.1	1.32 ± 0.2	1.39 ± 0.1
Liver/Body Wt: fasted (%)	M	4.04 ± 0.3	4.62* ± 0.1	4.91* ± 0.4	5.28* ± 0.2
	F	4.67 ± 0.6	4.68 ± 0.3	5.44* ± 0.3	5.43* ± 0.4
Liver/Brain Wt fasted (%)	M	2.55 ± 0.2	2.61 ± 0.2	3.04* ± 0.3	3.14* ± 0.1
	F	2.33 ± 0.3	2.29 ± 0.2	2.70 ± 0.3	2.62 ± 0.2
Liver Wt. nonfasted (g)	M	2.13 ± 0.2	2.22 ± 0.2	2.54* ± 0.3	2.95* ± 0.2
	F	1.68 ± 0.1	1.89 ± 0.2	2.18* ± 0.2	2.41* ± 0.2
Liver/Body Wt nonfasted(%)	M	5.72 ± 0.6	6.20 ± 0.4	7.03* ± 0.4	7.95* ± 0.6
	F	5.73 ± 0.2	6.27* ± 0.4	7.25* ± 0.2	8.02* ± 0.3
Liver/Brain Wt nonfasted (%)	M	4.18 ± 0.5	4.47 ± 0.4	5.00 ± 0.6	6.77* ± 0.6
	F	3.16 ± 0.2	3.84 ± 0.6	4.12* ± 0.3	4.63* ± 0.3
SGPT (U/L)	M	25**	42	40	40
	F	30***	34	44	68

*Statistically different ($p \leq 0.05$) from concurrent control value.
**Upper limit control value : 35 U/L. Incidence of individual values over maximum concurrent control value were 2/5 in low-, mid-, and high-dose males.
***Upper limit control value : 36 U/L. Incidence of individual values over maximum concurrent control were 1/5 low-dose and 3/5 mid- and high-dose females.

BEST POSSIBLE

Mortality and Clinical signs: no deaths in any gr. No sig drug related clinical signs.
B.wt, Wt change, Food intake: no consistent or dose-dependent effect noted in mean wt in any gr. Overall mean wt change in all male drug grs was reduced 16% and only 4-10% in female grs. This wt loss was considered drug related. There was no drug effect on food intake. [see figures below from sponsor].

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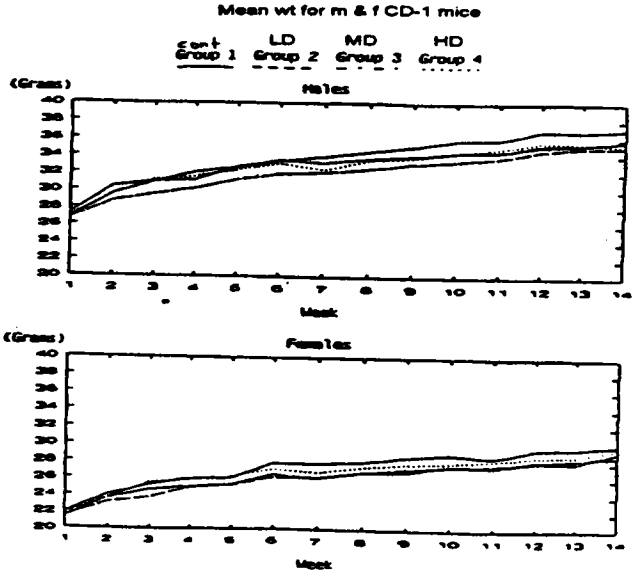

Hematology & Clinical Chemistry:

- Slight but sig decr in Hct in HDm (5%)
- slight non-sig incr in mean ALT in all male grs and MD&HDf. The individual values were ≥25% higher than the upper limit for the cont noted in 2-3 of 5mice/sex. However, these values (for HcT and ALT) were within the historical data provided by the sponsor. The mean AST values were dose-dependently but not sig incr in MD&HDf (18&21% respectively).

Organ wt:

Mean absol wt of the liver (non-fasted mice) incr sig and dose-depedently in MD&HDm&f (19&41% in m and 29&41% in f respectively). Absol wt in fasted mice incr dose-dependently in all 3 male grs but reached significance only in HDm (18% incr over the cont; 1.54±0.07g vs. 1.3±0.12g respectively); in MD&HDf the wt incr dose-dependently without reaching sig level. Rel wt of the liver (to B.wt) in non-fasted mice sig incr dose-dependently in MD&HD both sexes (22-40% in MD&HDm; 27-40% in MD&HDf) and in **LDf (10%)**. In fasted mice, the rel wt of the liver to B.wt was sig incr in all 3 male grs (16, 25%, and 33% respectively) and in MD&HDf at 16% but not in LDf. There was no sig change when liver wt was determined rel to brain wt in fasted mice and reached sig only in HDm&f and MDf of non-fasted mice. A non-sig but dose-dependent incr noted in the rel wt of the lung in all 3male grs/fasted (17, 20, 22% higher than the cont value, respectively) and the MD&HDf grs (8% higher than the cont for both grs).

Gross exam: no drug related findings.

Histopath: the changes in organ/tissue wts did not correlate with any histopath findings except for liver hypertrophy (centrilobular to midzonal) in MD&HD male and female mice that incr in severity with incr in dose. The hypertrophy correlated with the incr in absol and rel wt of the liver measured in fasted and non-fasted mice of these 2 higher doses.

Summary and Conclusion:

Dietary administration of modafinil to mice upto 60mg/kg did not affect mortality, clinical signs, food intake, hematology (except for a sig 5% decr in HDm HcT), clinical chem, or gross morphology. The only drug-related effect was an incr in absol and rel wt of the liver in males and females of the MD&HD (with 10% incr in LDf). This change was accompanied by centrilobular and midzonal liver hypertrophy that was dose-dependent in the 2 higher doses. Additionally, there was a small non-sig incr in ALT in all male grs and MD&HDf and dose-response non-sig incr in AST in MD&HDf. Although the values for ALT were within the historical data, they may still correlate with the liver enlargement.

From the TK study discussed below, data were highly variable and no data were detected in females except at HD and none at 60mg/kg for either sex. In males of MD&HD values ranged from bql of 0.5ug/ml to 2ug/ml. **The NOEL in this study is 60mg/kg**; there were no plasma levels detected at this dose which is the highest dose used in the mouse and rat carcinogenicity studies.

TK study in CD-1 mice/Study# DS-95-002/Report Issue date: Nov 1995/GLP.
CD-1 mice (10/sex/dose; 6-8wks old) were administered by dietary admixture, modafinil at 0, 60, 120, or 180mg/kg/d for 13wks. Blood was collected from *unfasted* mice within 1hr of the start of the am light cycle (6-7a.m.), from 5/sex/dose to determine modafinil, modafinil acid, and the sulfone. Of the 5 mice/sex/dose, 2 mice each were killed on days 93&94 and 1 on study day 95. Using validated reverse-phase HPLC method, plasma levels of modafinil, the acid, and the sulfone were determined.

Results:
Blood levels were analyzed by [redacted] The concentrations for all 3 cpds were very small and mostly near or below the ql of 0.50ug/ml and when values were recorded, they were highly variable. There were no values detectable in females except in HD where mean±s.d. of the parent was 0.51±0.47ug/ml. In males, the following values were recorded for the 2 high doses (ug/ml):

Dose	modafinil	modafinil sulfone
120	1.62±1.3	0.53±0.51
180	2.1±0.86	1.25±0.48

It is clear that these TK data did not support adequate level of exposure of mice to modafinil in this study and therefore, establishment of an MTD was not possible.

In a separate TK study (# DS-95-003), drug plasma levels were determined in CD-1 and OF-1 mice on days 1, 30, and 90 of treatment. Modafinil was administered by dietary admixture at 30, 60, 120, or 180mg/kg/d. On day of sacrifice, the admixture was replaced with basic control diet for at least 4hr followed by *gavage* of modafinil sol to these animals (modafinil was prepared in [redacted] oral suspension vehicle). Blood was collected at 1, 3, 6, 12, and 24hr post gavage. On day 1 of study, modafinil was administered by gavage prior to exposure via the diet, to provide PK data after a single dose. Parameters measured included: mortality, clinical signs, B.wt, food intake, macroscopic and liver organ wt (only on kill days 90/91). [lot# PA-009].

Note that this study did not have a concurrent control group.

Assignement of animals was as follows:

Dose(mg/kg) gavage/dietary	CD-1 m	f	OF-1 m	f
30	-	-	54	9
60	9	9	54	9
120	54	9	54	9
180	9	9	-	-

the 9mice/gr were used for determination of the C_{1hr} whereas, the 54 mice/gr were used for PK profile.

Results & Discussion:
There were no deaths, no signs, and no drug related findings in B.wt, wt change, food intake, or liver gross morphology in either strain. Absolute liver wt was minimally but dose-dependently incr in mice from both strains, rel liver wt was also slightly incr (dose-dependent) in both strains and sexes. Following single

administration, plasma levels of modafinil and its metabolites were similar between sexes and between the 2 strains. However, levels were quantifiable only upto 3-6hr postdose and only 2-3 plasma conc time points were available for analysis on days 1, 30, and 90. Therefore, values for AUC, Cl/F, and half life were approximations and used only for comparisons. TK results after repeate administration of modafinil are shown in the tables from the sponsor. These data provided limited info on repeate dose PK of modafininl. From the table below from the sponsor, it can be seen that the **C_{1hr} conc and AUC after repeate dosing (days 30 and 90) were decr and the clearance was incr to equal to or greater than the 45ml/min/kg hepatic plasma flow rate for a 20g mouse.** Because plasma levels were detectable only from 2-3 time points, the AUC, half life and Cl/F values could not be calculated and they are only approximations as mentioned above. The decr in modafinil conc with repeate dosing indicated incr of metabolism or saturation of metabolism and incr in drug Cl. Increase in parent metabolism is expected to incr the levels of its metabolites. This was not the case with modafinil, from tables 3&4, plasma levels of modafinil acid and sulfone in both strains were slightly decr or similar to the values on day1 (except for the CD-1 mice, plasma conc were slightly higher on days30&90 vs. day1). [redacted]

It is noted that absence of concurrent control gr in this study, made any definitive conclusions regarding drug related effects, difficult.

Table 2. Pharmacokinetic Parameters for Modafinil in Male CD®-1 and OF-1 Mice Following Daily Dietary Administration of Modafinil for 3 Months[a]

Study # D3-95-003

Strain	Day	Dose	C_{1hr}	$t_{1/2}$	AUC_{∞} or AUC_{24}[b]	CL/F	AUC_{∞}/Dose
		mg/kg/day	µg/mL	hr	µg•hr/mL	mL/min/kg	
CD-1	1	120	38.19	1.6	115.05	17.4	ND[c]
CD-1	30	120	21.70	ND	39.53	50.6	0.33
CD-1	90	120	19.30	ND	35.93	55.7	0.30
OF-1	1	30	7.79	0.9	15.65	31.9	ND
OF-1	30	30	4.20[d]	ND	ND	ND	ND
OF-1	90	30	4.31	ND	9.02	55.4	0.30
OF-1	1	60	18.98	1.1	47.49	21.1	ND
OF-1	30	60	7.74	ND	15.34	65.2	0.26
OF-1	90	60	12.97	ND	26.76	37.4	0.45
OF-1	1	120	37.83	1.8	115.16	17.4	ND
OF-1	30	120	17.51	ND	40.02	50.0	0.33
OF-1	90	120	21.28	ND	40.30	49.6	0.34

[a] Days 1, 30, and 90 modafinil doses were administered by oral gavage. Pharmacokinetic parameters were calculated using mean data from 3 animals.
[b] AUC_{∞} applies to Day 1 and AUC_{24} applies to Days 30 and 90.
[c] ND, not determined.
[d] Modafinil plasma level was only quantifiable in the one-hour post-dose sample.

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Table 3. Pharmacokinetic Parameters for Modafinil Acid in Male CD®-1 and OF-1 Mice Following Daily Dietary Administration of Modafinil for 3 Months[a]

Strain	Day	Dose mg/kg/day	C_{1hr} µg/mL	$t_{1/2}$ hr	AUC_{∞} or AUC_{τ}[b] µg•hr/mL
CD-1	1	120	6.59	1.7	21.62
CD-1	30	120	14.61	ND[c]	32.17
CD-1	90	120	10.10	ND	19.90
OF-1	1	30	1.40[d]	ND	ND
OF-1	30	30	1.02[d]	ND	ND
OF-1	90	30	1.49[d]	ND	ND
OF-1	1	60	3.72	1.5	10.11
OF-1	30	60	2.44[d]	ND	ND
OF-1	90	60	3.98	ND	8.32
OF-1	1	120	5.84	1.9	19.20
OF-1	30	120	5.36	ND	11.84
OF-1	90	120	7.63	ND	13.92

[a] Days 1, 30, and 90 modafinil doses were administered by oral gavage. Pharmacokinetic parameters were calculated using mean data from 3 animals.
[b] AUC_{∞} applies to Day 1 and AUC_{τ} applies to Days 30 and 90.
[c] ND, not determined.
[d] Modafinil acid plasma levels were only quantifiable in these one-hour post-dose samples.

BEST POSSIBLE

Table 4. Pharmacokinetic Parameters for Modafinil Sulfone in Male CD®-1 and OF-1 Mice Following Daily Dietary Administration of Modafinil for 3 Months[a]

Strain	Day	Dose mg/kg/day	C_{1hr} µg/mL	$t_{1/2}$ hr	AUC_{∞} or AUC_{τ}[b] µg•hr/mL
CD-1	1	120	5.63	4.7	99.62
CD-1	30	120	8.73	ND	25.20
CD-1	90	120	9.88	ND	27.85
OF-1	1	30	2.08	2.6	12.44
OF-1	30	30	1.22	ND	4.17
OF-1	90	30	1.33	ND	4.00
OF-1	1	60	4.02	8.6	39.40
OF-1	30	60	2.38	ND	8.17
OF-1	90	60	3.57	ND	10.91
OF-1	1	120	7.83	2.7	86.49
OF-1	30	120	8.19	ND	38.84
OF-1	90	120	8.73	ND	38.61

[a] Days 1, 30, and 90 modafinil doses were administered by oral gavage. Pharmacokinetic parameters were calculated using mean data from 3 animals.
[b] AUC_{∞} applies to Day 1 and AUC_{τ} applies to Days 30 and 90.
[c] ND, not determined.

Conclusions:
This TK study in 2 mouse strains following repeate dosing of modafinil provided limited info on PK. Modafinil was shown to be high clearance cpd in mice and induces its own metabolism after repeate dosing as seen from decr levels and exposure. Incr in modafinil metabolism did not incr levels of its metabolites. This suggests additional metabolic pathways which was later confirmed by the sponsor to be a hydroxylation mechansim. The PK profile seemed to be dose-independent between 30-120mg/kg. The TK parameters were comparable between the 2 strains, CD-1 & OF-1, mice.

Rat:
The following rat subchronic tox studies are Non-GLP (unless noted otherwise) and conducted during 1980, 1981, and 1987 in the labs of [redacted] Generally, non-GLP studies are not reviewed and their material are not taken into consideration unless the deviations from GLP are listed and considered to be of no sig impact on the conduct and results of the study. However, for the purpose of completion of the review of the toxicity of modafinil, a brief discussion is provided below.

- 4wk oral gavage study in rats with 4wk reversibility period/1980/Non-GLP/ DS-93-006.

Strain/No. per gr: SD, 10/sex/dose; 6/sex/dose for recovery study.
Doses (mg/kg/d): 100, 200, 400; cont dosed the vehicle of 0.25% gum arabic.

Parameters assessed: mortality, clinical signs, B.wt, food intake, water intake, urine (pH, osmolarity, density, vol.), hematology, clinical chem, hepatic function test (sulfobromophthalein Cl checked on wk4 in 5/sex/gr), gross exam, organ wt, and histopath (for cont and HD only and any gross lesions noted in other grs). ANOVA and Student's t-test were used to analyze the data.

Results:
Only drug related findings are listed below:
Mortality: 1HDm on d4 cause unknown; 1HDm recovery gr on day1 of recovery cause unknown. Three more deaths in HD&cont gr due to accidents.
Clinical signs: hypersalivation in HD from d11 till end of study.
B.wt/Food intake/water: slight non-sig decr in mean wt of HDm (about 5% of cont) starting on d15 till end of study. No effect on food intake except for a sig ($p<0.05$) 11% decr from the cont on d3 of study in HDm but food intake incr and was higher than the cont by end of study. Water consumption was incr in HDm throughout the study reaching statistical sig on d3&23 (9-31ml more than cont on these days), and in HDf on d23 (16ml more than the cont on this day).
Hematology: macrocytic anemia observed in HDm&f and some parameters in MD gr: RBC decr 4&15% in MD&HDm/13% in HDf.
Hb decr 11% in HDm/5&7% in MD&HDf.
Hct decr 7% in HDm/5% in HDf (did not reach sig level).
MCV incr 8% in HDm/7% in HDf.
Leucocytes incr 41% (14.4 vs. 10.2 in cont) in HDf/45% (20.5 vs. 14.1 in cont) in HDm (did not reach sig level).
Neutrophils incr 2x in HDf/1.6x in HDm (did not reach sig level).
Urine: the only effect was acidic urine in HDm&f from wk2 till end of study.
Gross exam: dark spleens in 7/20MD and 14/20HD vs. 3/20cont.
Organ wt: dose-dependent incr in absol liver wt (MD&HDm&f) and absol spleen wt (MD&HDm; HDf); absol wt of the thymus was decr in HDm and in all 3f gr (non-dose dependetly and not sig). The decr ranged between:

Liver	11-27% m	10-31% f
Spleen	16-40% m	41% f
Thymus	22% m	9-17% f

Relative wt of the liver was also incr dose-dependently in all 3 male gr and MD&HDf and spleen wt incr dose dependently in MD&HDm and HDf; relative wt of the thymus was decr in HDm. The decr ranged between:

Liver	7-33% m	12-29% f
Spleen	15-47% m	36% f
Thymus	18% m	

Histopath: no findings in any organ/tissue examined.

Any of the above findings reported during the study were reversed during the recovery period.

Conclusion: oral gavage administration of modafinil to rats for 4wk at 100, 200, and 400mg/kg caused hypersalivation in HD rats, macrocytic anemia in HD and some hematology parameters decreased in MD, acidic urine in HD, enlarged liver and spleen in MD&HD (absol & rel), decr in thymus wt (absol & rel), and dark spleen in MD&HD rats. The organ wt changes and gross findings did not correspond to histopath changes. The **NOEL is 100mg/kg**.

- 12wk oral gavage study in rats with 4wk reversibility period/1981/Non-GLP/ DS-93-007

Strain/No. per gr: SD, 16/sex/dose; 10/sex/dose for recovery study.
Doses (mg/kg/d): 50, 100, 200; cont dosed the vehicle of 0.25% gum arabic.

Parameters assessed: mortality, clinical signs, B.wt, food intake, water intake, urine (pH, osmolarity, density, vol., electrolytes), hematology, clinical chem, hepatic function test (sulfobromophthalein Cl checked on wk4 in 5/sex/gr and12), kidney Cl (p-aminohippuric acid), gross exam, organ wt, and histopath (for cont and HD only and any gross lesions noted in other grs).
Tests were done on wks6/7 and 13 of study. ANOVA and Student's t-test were used to analyze the data.

Results:
Only drug related findings are listed below/all findings are statistically sig unless specified otherwise):
Mortality: none in HD, 1 LD killed moribund due to crusted cyst in the cheek but splenomegaly was found on exam.
Clinical signs: hypotonicity in HDm.
Hematology: 6wk (MD was not examined): MCV incr 3% in HDm&f; lymphocyte incr 23% in HDm; reticulocyte incr 2x in HDf.
13wk: RBC count decr in HDm&f (8&12%) and Hb decr in HDm&f (6&8%); reticulocyte was incr 2x in HDf.
Clinical Chem: cholesterol was incr 1x in LD&HDm&f at wk6 (MD was not examined); at 13wk: cholest incr in HDm (17%), creatinine decr 16-19% in HDm&f; and protein incr 6% in HDm.
Hepatic Function: Cl was accelerated in HDf on wk4; and in MD&HDm&f and LDm on wk12.
Gross exam: no findings.
Organ wt: absol & rel wt of the liver incr in MD&HDm and HDf (only absol wt), absol & rel wt of spleen and kidneys incr in HDm, the absol wt of the thymus was decr 16% in HDm, absol wt of the adrenals was decr 18% in HDf.

Liver	13-25% (15-30%) m	17% (19% not sig) f
Spleen	19% (25%) m	-
Kidneys	10% (15%) m	-

Values in () are the changes in rel wt compared to the cont. The wt was relative to 100g B.wt.

Histopath: no findings in any organ/tissue examined.

Any findings reported during the study were reversed during the recovery period except for an incr in absol wt of the liver in LDf (14%) which was absent during the treatment period.

Conclusion: oral gavage administration of modafinil to rats for 13wk at 50, 100, and 200mg/kg caused hypotonicity in HDm, incr reticulocyte 2x in HDf during wk6&12, incr in cholesterol 17% in HDm&f at wk6&wk12, on wk12: creatinine decr in HDm&f and protein incr in HDm. Hepatic Function was accelerated in HDf on wk4; and in MD&HDm&f and LDm on wk12. Absol & rel wt of the liver incr in MD&HDm and HDf (only absol wt), absol & rel wt of spleen and kidneys incr in HDm, the absol wt of the thymus was decr HDm and absol wt of the adrenals was decr in HDf. None of the organ/tissue wt changes corresponded to histopath findings. **The NOEL is 100mg/kg.**

- 13wk oral dietary study in rats/1987/GLP/DS-95-004

Strain/No. per gr: SD, 10/sex/dose.
Doses (mg/kg/d): 25, 75, 100, 150; cont administered cont diet.

Parameters assessed: mortality, clinical signs, B.wt, food intake, ophthalmology (cont and HD only), hematology, clinical chem, gross exam, organ wt (pituitary, thyroid,/parathyroid, adrenals, liver, kidneys, spleen, and heart), and plasma level (blood collected at wk10 of study; data sent to sponsor for analysis)**(No TK analysis was done).** Histopath: organs/tissues were fixed in formalin but no histopath was done. All tests were done at end of 12wk of study. ANOVA, Dunnett, and Student's t-test were used to analyze the data.

Results:
Hematology: Hb* decr 3-7% in all male drug grs non-dose dependently; reticulocyte count incr 0.7-1.7x the cont in males dosed 25, 75, 150mg/kg; RBC* count decr 5-6% in males dosed 100&150mg/kg.
Clinical Chem: cholest* incr dose-dependently in all male (8-50%), and female (18-42%) drug grs; protein* content incr in males (4-9%) dosed ≥75mg/kg; creatinine* decr in males dosed ≥75mg/kg and

females (9-13%) dosed 100&150mg/kg; and urea* incr 12% in males dosed 150mg/kg.
Organ wt: rel liver wt incr (19-35%) in males dosed ≥75mg/kg and in females (14%) dosed 150mg/kg and rel kidney wt incr in 150mg/kg males (16%) and females (12%).

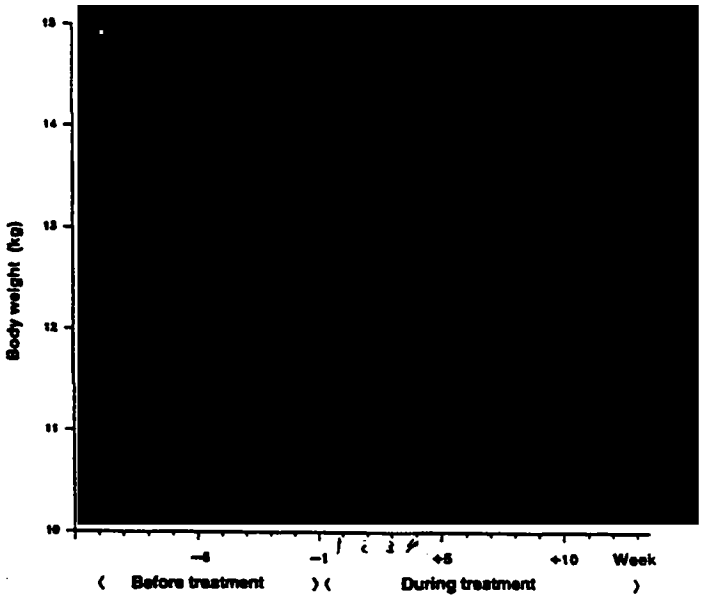
* These values were within historical data for this strain; the value for cholest in HDm was outside the historical range. No historical data for reticulocytes were provided.

Conclusion:
Oral dietary administration to rats for 13wks at 25, 75, 100, or 150mg/kg caused changes in hematology and clinical chem parameters that reached statistical sig but were within the historical data except the incr in choles noted in HDm. The rel wt of the liver incr in HDf and in males dosed ≥75mg/kg and the rel wt of the kidneys was also incr in m&f dosed 150mg/kg; no other findings. The **NOEL is <75mg/kg.**

Dog
- 12wk oral gavage in beagle dogs/DS-93-010[redacted]**Non-GLP/1980-1981.**
No. per gr: 3/sex/dose.
Doses (mg/kg/d): 20, 50, and 100mg/kg/d for 12wks. **The 100mg/kg dose caused severe adverse effects (see below) and was decr to 75mg/kg after 2wks of initiation.** Dose was in cachets.

Parameters assessed: mortality, clinical signs, B.wt, food intake, CVS (HR, BP, EKG), neurological exam (reflexes), ophthalmology (cont and HD only on wk6 and all gr at end of studt), hematology, clinical chem, urinalysis, gross exam, organ wt (brain, thyroid, adrenals, liver, kidneys, spleen, pancreas, lungs, tibia, thymus, gall bladder, eyes, ovaries, prostate, testicles, and heart),**No TK analysis was done.** Histopath: organs/tissues were fixed in formalin and stained with H&E. Function tests: hepatic (sulfobromophthalein clearance test and Renal: concentration test (vol and urine density).

Results:
Mortality: one male dog dosed 100mg/kg was killed after it lost 4.6kg in 2wks, necropsy showed kidney necrosis with hemorrhagic areas. No other deaths.
Clinical signs: all 100mg/kg and 75mg/kg dogs showed motor excitation with stereotypy head movements, panting and sometimes hypotension. These signs seen 3hr postdose and remained severe upto 3hr later, but subsided by 24hr. At 75mg/kg agitation was also seen in addition to stereotypy; signs diminished by end of study wks11-12. At 50mg/kg the same above signs were seen in 5/6 dogs. No clinical signs were observed at 20mg/kg upto 7wks of dosing. On wk8 and till end of study, slight agitation and stereotypy was seen in all dogs.
B. Wt & Food:



From the above figure, it is clear that wt decr in all 3 drug grs starting from wk2 till end of study. The decr was dose-dependent on wks 2,3, and 4: 450g in LD, 570g MD, and 1340g HD loss in wt. Food intake per day was incr on wk5 but the wt loss did not recover and no gain at all was seen in HD. Appetite was decr in MD&HD from wk8 and till end of study.

CVS: no effect on MAP and HR decr on wks6&12 in HD. At this time, the QT interval was sig incr in HD but no change in QRS. Only 1LDm showed pronounced bradycardia accompanied by electrical disturbances (not specified). QT in HD on wk6 was 17 vs. 13 in cont and on wk12, it was 18 vs 15 1/sec in cont.

Neurological exam: no effect on the patellar, pupillary, and visual and tactile reflexes.

Ophthalmology: irreversible opacity was seen in 1MDm and 3HD dogs (2f, 1m).

Hematology: the following changes reached statistical sig and are considered drug related:

- ⇑ MCV in HD wk12 (70 vs. 67picog in cont); no change in RBC count.
- ⇑ WBC count & neutrophils in HD on wk12,
- ⇓ in 24hr sedimentation rate dose-dependent in MD&HD at 24hr samples.
- ⇑ in platelet count in MD&HD non-dose dependent (418&411 vs. 303 in cont).

One HDm showed clear macrocytic anemia; high WBC count was already seen in pre-drug measurement.

Clinical Chem: the following changes reached statistical sig and are considered drug related:

- ⇑ ALP in HD wk6 (141 vs. 42u/l in cont) and in MD&HD wk7 (60&116 vs. 40 in cont), and dose-dependently in all 3 drug grs on wk13 (58, 110, 135 vs. 30u/l in cont).
- ⇑ lipids in HD wk6&7 and MD&HD wk13 (non dose-dependent)(1.4x cont).
- ⇑ cholesterol HD wk7 and MD&HD wk13 1.4-2.8x cont).

Urinalysis: small but sig incr in urine density in HD on wks6&12. No other changes.

Organ wt and Macroscopic Exam: there were changes in absol and rel wt of several organs including the liver, however, mean wt gain was sig reduced which might have been responsible for these changes. No gross changes.

Histopath: no drug related findings.

Conclusion:

Oral administration of modafinil to dogs for 13wk caused severe clinical signs to include stereotypy with head movement, agitation, panting and sometimes hypotension. One male dog dosed 100mg/kg was killed due to sig loss in wt by wk2, this led to decr the dose to 75mg/kg. These clinical signs remained upto 5hr postdose but subsided by 24hr postdose. All three drug grs los wt from wk2/3 till end of study although food intake was unaffected. Bradycardia was seen in HD and QT interval was sig incr without an effect on QRS; MAP was not affected. Irreversible corneal opacity was seen in 1MDm and 3HD dogs. There were several hematology and clinical chem parameters that reached statistical sig and considered drug related: ⇑ in MCV in HD (no change in RBC count), ⇑ WBC count & neutrophils in HD, ⇑ platelet count non-dose-dependent in MD&HD,⇓ in 24hr sedimentation rate dose-dependent in MD&HD at 24hr samples,⇑ platelet count in MD&HD non-dose dependent, ⇑ ALP in HD wk6 and in MD&HD and, dose-dependently in all 3 drug grs on wk13, ⇑ lipids in HD wk6&7 and MD&HD wk13 (non dose-dependent), and ⇑ cholesterol in HD wk7 and MD&HD wk13. The changes in organ wts were considered secondary to wt loss. There were no gross or histopath findings. **A NOEL could not be determined due to the clinical signs and wt loss in the 20mg/kg dose.**

Summary of Subchronic Studies:

In general, oral dietary or gavage administration of modafinil to mice or rats was well tolerated at the doses tested and upto 13wks of administration. There were no drug-related deaths in mice or rats at any dose. The main findings in mice and rats (unless indicated otherwise) include:

- Dose-dependent incr in liver wt (absol and/or rel) in both sexes at doses ≥25mg/kg in mice and ≥75mg/kg rats. This incr in liver wt was accompanied by incr in serum ALT and liver hypertrophy in one study in mice (13wk dietary); histopath was no observed in any other subchronic rat or mouse study.
- Dose-dependent incr in spleen wt and kidney at ≥200mg/kg rat 4wk &12wk gavage study.
- Decr in thymus wt in m and/or f in rat 4wk & 12wk gavage study.
- Some hematological changes in both species such as macrocytic anemia in m+f rats dosed 400mg/kg modafinil by gavage for 4wks, decr in Hb, in both species, incr in reticulocyte no. in both species at ≥25mg/kg male rat grs and both sexes of rats dosed 200mg/kg, and in mice dosed ≥75mg/kg.
- The NOEL in mice was 60mg/kg in a 13wk dietary study and 75 and 100mg/kg in rats dosed for 4 or 13wks by either gavage or dietary.
- Blood levels and TK parameters of modafinil and/or its acid and sulfone metabolites, were measured only in recently conducted 3mo mouse studies; none was done in the rat subchronic studies. In the first study, values were to be measured on wk4, 30, and 90 but due to technical problems, values were measured only during wk4. However, the values were below quantitation limit of 0.5ug/ml in all grs except in males dosed 180mg/kg at 2ug/ml. The 1hr modafinil plasma levels on d30&90 were lower than the values measured on day1 (after a single dose). This indicated autoinduction or saturation of metabolism with incr in Cl/F. From data in this and other tox studies, modafinil has been shown to induce its own metabolism. As a consequence of incr in parent metabolism, the palsma levels of the metabolites are expected to incr. However, this was not the case in this 13wk mouse study. It was proposed by the reviewer and later confirmed by the sponsor, that other metabolic pathway(s) (in this case hydroxylation) may be operative.
- Based on the blood level data, it was concluded that 60mg/kg dose tested in the mouse car study was not an MTD. The findings in this 3mo study were equivalent among all the 3 doses tested except for enlarged liver in MD&HD, and based on this, at least 180mg/kg dose could have been tested in the car study.

- Dogs treated for 13wk had stereotypy at doses ≥20mg/kg with head movement, agitation, panting, and sometimes hypotension at 100/75mg/kg dose. Mean wt gain was sig decr in all drug grs without an effect on food intake. Irreversible corneal opacity was observed in 1 dog dosed 50mg/kg and 3 out of 6 dogs dosed 100/75mg/kg. Some changes in hematology and clinical chem that reached statistical sig and considered drug related included incr in MCV, platelet, and WBC, incr in cholest., lipids, and ALP. There were no gross or histopath. There were organ wt changes but considered secondary to wt loss. A NOEL could not be determined in this study due to clinical signs and wt loss at 20mg/kg dose.

CHRONIC TOXICITY:

All studies were GLP
- 26-week oral study in rat
- 52-week oral study in rat
- 52-week oral study in dog

Rat
26-week rat:
Sprague-Dawley rats (20/sex/dose) were orally (by gavage) administered MDF at doses: 20, 50, 200 mg/kg/d for 26 wks.
Clinical signs: salivation immediately after dosing in MD and HD, and slight hypersensitivity (not specified) in females of all doses (majority of HD and some MD and LD).
Mortality: total of 4 considered by the sponsor to be drug unrelated. HD male sacrificed on wk 23 showed pallor of extremities and limited use of hind feet, lost 22 g weight; autopsy showed enlarged spleen, pale kidneys, and a small flaccid left testis. Male administered LD found dead on wk 22 without prior ill signs; autopsy showed large liver. Female of HD died on wk 3 was emaciated from wk 1, had swallen and firm left side of abdomen, autopsy showed enlarged and cystic kidneys with subcapsular discoloration. HD male died immediately postdose on wk1, prior to death animal showed severe respiratory distress, convulsions, and salivation, autopsy showed minimal congestion in lymph nodes and dark liver.
Body weight: wk 13-26 rats of all groups dose-dependently, gained slightly less weight than the control group, statistical significance reached only in HD females.
Hematology: changes were not dose-dependent, transient, and not comparable in both sexes. On several treatment wks including wk 24 small but significant changes were noted relative to the control: PCV was slightly less in HD males and females and small decrease in Hb and RBC noted in HD females. Reticulocyte number was increased over the normal control value only in HD males.
Urinalysis: no drug related changes.
Clinical Chemistry: no drug related changes except for a significant increase in cholesterol of HD males.
Ophthalmoscopy: no drug related changes.
Organ Weight: significant increase in liver, spleen, and kidney weights of HD males.
Macroscopic Examination: enlarged liver in HD males only.
Histopathology: [see table]: in all male treatment groups the adrenals had minimal increase in cytoplasmic vacuolation or foamy change (rarefaction) in the zona fasiculata. Signs of progressive glomerulonephrosis noted in HD males is considered part of old age. Sublobular foci of altered hepatocytes were found in HD males. Since the incidence is low, the toxicological significance of this lesion is unclear.

It is concluded **that a NOEL could not be established and 20 mg/kg is the LOEL based on renal and adrenal histopathology.**

26wk rat tox:

Histopathological lesion incidence table

Number of rats with:	Group							
	1♂	2♂	3♂	4♂	1♀	2♀	3♀	4♀
Liver								
Centrilobular vacuolation/rarefaction	15	6	2	13	2	-	3	7
Generalised vacuolation	-	-	-	-	1	-	-	-
Periportal vacuolation	-	-	1	2	1	-	-	-
Periportal fat Oil Red O	-	-	-	2	1	-	-	-
Fibrosis/necrosis	-	-	-	1	1	-	-	1
Altered vacuolated hepatocytes	-	-	-	3	-	-	-	-
Bile duct hyperplasia	-	-	-	-	1	-	-	-
Inflammation/siderocytes/mononuclear cells	1	1	-	-	1	2	-	2
Sinus congestion	8	1	-	3	-	-	-	-
Pericholangitis	-	-	-	1	-	-	-	-
Kidneys								
Hydronephrosis	-	-	-	-	-	-	-	1
Pyelonephritis	-	-	-	-	-	-	-	1
Dilatation of renal pelvis	2	-	2	-	1	2	3	-
Basophilic/dilated cortical tubules/ nephritis	-	4	2	9	-	-	3	6
Dilated Bowman's capsule	-	-	-	2	-	-	-	1
Perivascular lymphoid aggregations/ cuffing/inflammatory cells	-	1	1	3	-	-	-	-
Adrenals								
Dilated/medullary sinusoids	-	-	-	-	-	-	-	1
Focal necrosis	-	-	-	-	-	-	-	1
Vacuolated zona fasciculata/cortical vacuolation	3	3	5	8	-	-	-	-
Foamy change	1	4	3	2	1	-	1	-
Prominent zona reticularis	-	2	-	3	-	-	-	-
Number of rats examined	20	20	20	20	20	20	20	20

52-wk rat dietary: This study is part of a 104-wk oncogenicity study; only the 52-wk interum toxicity data are reported here.
Strain: Sprague-Dawley, 20/sex/dose
Study No. DS-93-009/Laboratory: [redacted]
Doses: 6, 30, 60 mg/kg/d for 1 yr. The 6mg/kg was selected based on the human dose of 400mg/d (6.7mg/kg based on 60kg). The mid and high doses were chosen based on a 13-wk dietary study in SD rats using 25, 75, 100, and 150 mg/kg (see subchronic section). Results of 150 mg/kg showed increases in BUN, increased liver wt in f and kidney weight in m and f, and in 75, 100, and 150mg/kg protein levels and liver wt increased and creatinine level decreased in m and f.
Clinical Signs: no drug-related changes/no tables or any further details were provided.
Mortality: 1 male each in LD and MD and 2/20 males in HD. Only the death of one HD male maybe drug related, the rest were accidental.
Body weight/food and water consumption: generally, no significant drug-related changes. HD males showed a tendency toward smaller weight gains than the control over the 52-wk period; this effect was considered drug-related.
Hematology: slight but significant decrease at wk 52 in Hb, PCV, RBC, total WBC count and to a lesser extent eosinophil and neutrophil counts, in HD males. These effects as reported by the sponsor, were contributed to the decrease in B.wt. The values were within the normal range for this strain therefore, of unclear toxicological value.
Urinalysis: no drug-related changes.
Blood Chemistry: slight increase in total, free, and esterified cholesterol levels of MD and HD males and/or females on wks 26 and/or 52.
Organ weights: increase in liver weight in MD and HD and increase in kidney and spleen weights of HD rats (m+f, absolute and/or relative weights).
NOEL is 6 mg/kg.
Macroscopic examination: no drug-related changes.
Histopathology: no drug-related changes. Histopathology was conducted in all animals of the control and HD; liver, lung, and kidneys of all animals in LD and MD, and all dead or moribund rats.

Summary and Conclusion:
Modafinil administered at 6, 30, or 60mg/kg/d in the diet to m and f SD rats for 52wks caused no drug-related mortality, a slight decrease in body weight gain in males, and slight but siginifcant decrease in Hb, PCV, RBC, total WBC counts. Also, cholesterol level (total, free, esterified, and sometimes triglycerides) was slightly increased in some m and f of mid and high doses. Liver, kidney, and spleen weights (relative and/or absolute) were slightly increased in mid and high doses of both sexes. No effects were noted in rats dosed 6 mg/kg therefore considered to be the NOEL.

Comment: although some hematology, clinical chemistry, and organ weight changes occurred in the two high doses, it is the opinion of the reviewer that the dose was not pushed high enough. This is evident in the 13-wk study, at which marked effects were not seen at 150 mg/kg.

It is worthy to mention that in the 12-wk rat non GLP study, any drug-related changes were reversible except for the increased liver weight in 200 mg/kg dosed females that remained high.