Rat 3mo dietary (Cont.)

Organ wt/Gross & Histopath: mean absol and rel wt of the liver were incr in HDm&f rel to the cont (table below from sponsor). These changes in liver wts were accompanied by centrolobular hypertrophy in all 10/10 HD rats.

Male Rats — Doses mg/kg/d

PARAMETER (MEAN)	0	1	3	10	32	100
BODY WEIGHT (S.D.)(GRAMS)	511.01 (20.9)	523.93 (30.50)	527.00 (50.73)	528.54 (45.58)	516.40 (25.67)	494.92 (36.29)
ABSOLUTE LIVER WEIGHT (S.D.) (GRAMS)	19.2976 (2.6177)	20.9815 (3.0006)	20.6986 (3.3647)	21.7105 (3.4529)	19.6699 (1.5870)	22.4756** (3.0420)
RELATIVE LIVER WEIGHT (S.D.) (%B.W.)	3.7738 (0.4643)	3.9945 (0.4258)	3.9238 (0.4734)	4.1091 (0.5785)	3.8095 (0.2334)	4.5284*** (0.3661)
CENTROLOBULAR HYPERTROPHY (INCIDENCE)	0/10	0/10	0/10	0/10	0/10	10/10

female rats — Doses (mg/kg/d)

PARAMETER (MEAN)	0	1	3	10	32	100
BODY WEIGHT (S.D.)(GRAMS)	306.98 (14.26)	301.94 (21.18)	308.15 (19.19)	328.57 (30.30)	310.53 (20.69)	284.46*** (19.47)
ABSOLUTE LIVER WEIGHT (S.D.) (GRAMS)	11.6290 (1.2628)	11.3700 (2.0238)	11.6917 (1.4799)	12.4322 (1.2382)	12.4662 (1.4684)	13.1422** (1.2040)
RELATIVE LIVER WEIGHT (S.D.) (%B.W.)	3.7870 (0.3653)	3.7607 (0.5786)	3.7914 (0.3967)	3.7935 (0.3264)	4.0167 (0.4008)	4.6209*** (0.2821)
CENTROLOBULAR HYPERTROPHY (INCIDENCE)	0/10	0/10	0/10	0/10	0/10	10/10

** sig at p<0.02 ***sig at p<0.01

APPEARS THIS WAY ON ORIGINAL

Rat 3mo Dietary tox study (Cont.)

Table below represents drug plasma range and mean±s.d. of C_{max} on days 7&86:

Dose (mg/kg/d)	Range (mean ±s.d.) in ug/ml			
	m	f	m	f
	Day 7		Day 86	
1	<0.005-0.02 **(0.01±0.01)**	<0.005-0.02 **(0.02±0.00)**	<0.005-0.06 **(0.04±0.01)**	<0.005-0.04 **(0.03±0.01)**
10	0.02-0.22 **(0.17±0.06)**	0.02-0.30 **(0.26±0.02)**	0.03-0.45 **(0.33±0.10)**	<0.005-0.47 **(0.36±0.05)**
100	0.02-4.0 **(4.0±0.46)**	1.30-6.60 **(4.11±2.43)**	0.34-6.0 **(4.60±1.20)**	0.42-7.50 **(6.0±1.36)**

The range of plasma conc for the metabolite (CL 284-859) were <0.005-8ug/ml on d7 and <0.005-11ug/ml on d87.

Table below from the sponsor, shows AUC and T_{max}:

PK in rat after dietary dosing for 3mo CL 284,846 (Parent)

Day 7					Day 86			
Dose (mg/kg/day)	Sex	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (µg.hr/mL)	Dose (mg/kg/day)	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (µg.hr/mL)
1 (1.1)*	Male	0.01	0-12	0.13	1 (0.9)*	0.04	4	0.39
1 (1.1)*	Female	0.02	8	0.20	1 (0.8)*	0.04	4	0.34
10 (12.4)*	Male	0.17	4	2.37	10 (9.6)*	0.33	4	4.81
10 (10.8)*	Female	0.26	12	3.24	10 (9.0)*	0.36	8	4.78
100 (124)*	Male	3.85	8	56.1	100 (106)*	4.57	8	51.5
100 (128)*	Female	4.11	4	77.9	100 (118)*	5.86	4	90.2

CL 284,859 (Metabolite)

Day 7					Day 86			
Dose (mg/kg/day)	Sex	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (µg.hr/mL)	Dose (mg/kg/day)	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-24} (µg.hr/mL)
1 (1.1)*	Male	<0.005	NA	NA	1 (0.9)*	0.02	4	0.32
1 (1.1)*	Female	<0.005	NA	NA	1 (0.8)*	0.01	4	0.11
10 (12.4)*	Male	0.1	4	1.49	10 (9.6)*	0.38	8	5.82
10 (10.8)*	Female	0.14	12	1.70	10 (9.0)*	0.23	4	3.27
100 (124)*	Male	6.99	12	100.1	100 (106)*	10.29	8	168.8
100 (128)*	Female	4.79	12	77.6	100 (118)*	6.72	8	111.6

NA = Not Applicable

Calculated from mean (n=3 rats/timepoint/sex) plasma concentrations

*Values in parenthesis are the actual dose based on food consumption

Plasma conc of the parent incr linearly with dose (except in HDm&f on d7). Exposure on the other hand, incr more than proportional to the dose in both males and females for both periods. Compared to the parent, metabolite conc and exposure incr non-linearly with dose on both periods. There seemed to be drug accumulation, as seen from higher conc and exposure for both the parent and metabolite, on d86 compared to the corresponding values on d7. At the HD, metabolite conc and exposure, were greater than those of the parent on both periods.

It is concluded that oral dietary daily administration of CL-284,846 to rats for 3mo was tolerated upto 100mg/kg without death or clinical signs. The **NOEL is 32mg/kg** since mean wt gain, liver wt, and liver histopath were observed in the 100mg/kg dose grs. Mean plasma level of the parent at 100mg/kg was 6ug/ml (range 0.02-7.5ug/ml) and mean exposure was 90ug.hr/ml. The conc and exposure for both the parent and metabolite were higher on d86 than the corresponding values on d7. This is indicative of drug accumulation.

- 3 month oral **gavage** study (# 89291, 89324)(Index#23438)
  Study Initiation Date: 11/1989 Lab: [redacted]

Doses: **5, 50, 200mg/kg/d**; control received the vehicle: carrier*/polysorbate.
Strain/No./Sex/Dose: Sprague Dawley/10/sex/dose; additional 15/sex/dose were used for TK.
Parameters assessed: mortality, clinical signs, B.wt/wt gain, food intake, ophthalmology, hematology, clin chem, urinalysis, TK, organ wts, gross exam, and histopath of all organs/tissues. Bone marrow smears were evaluated from all rats at end of study. Electron microscopy for liver was done on all rats (3/sex/dose) in cont and HD.

* carrier consisted of methocel which is methyl cellulose 0.5% and Tween 80 at 0.1% in water.

Basis for dose selection: the HD of 200mg/kg/d was based on a previous study where 300mg/kg caused mortality whereas, 200mg/kg caused only elevated serum enz, incr liver wt, and hepatocyte "swelling". The LD of 5mg/kg and MD of 50mg/kg are 29 & 294 multiples of the maximium human dose of 10mg/d (0.17mg/kg), respectively.

Results:
Mortality & Clinical Signs: death occurred as follows:
LD 1/10m study day 16; 2/10f study days 40&86
MD 2/10m study days 1&86
HD 9/10f study days 1,2,3,&13 (8 of these 10 females died within the 1st 3 days of study. Hypoactivity and ataxia seen in all rats shortly postdose. Prostration seen in most HDf and 4HDm, also in HD during wk7 of dosing, convulsions occurred in 3m & 1f during dosing. Wet/stained peri-anal area noticed in both sexes dosed HD.

Rat 3mo gavage (Cont.)

B.wt/Food Intake: no drug effect on food intake in any gr., the incr noted in food consumption was due to food wasting since rats did not finish eating the pellets and the latter fell out from the cage. Mean B.wt in males was sig decr in HD and remained sig decr till end of study, these decreases ranged between 7-10% of the cont at the given time period. Mean B.wt in females was not sig affected by drug dosing. Mean B.wt gain was sig decr in MD&HDm during the 1st few weeks of dosing, the decr ranged between (% of control): 4-68% and, during days 84-91, HDm lost 9g represnting -220% wt change rel to the cont. Mean wt gain in females was sig decr at the LD&MD and remained low till end of study, these decr ranged between 36-83% of the cont. Females in HD lost wt rel to the cont during d49-56 (-56% of cont), and, -310% of cont during d63-70, and both MD&HD female grs showed -1200&1000% loss rel to cont respectively, during the last 2wks of study. The only female survivor in HD had an incr in mean B.wt.
Ophthalmology & Urinalysis: no drug effect.
Hematology: no sig or dose-dependent changes noted in any parameter. The following were small effects but reached statistical sig and observed in one sex and were not dose-dependent. Small decr in RBC, Hb, and Hct (6-15% of cont), mild incr in MCV on days 35&90 in HD (1x cont), mild incr in WBC (25-35% over cont) mainly due to lymphocytes noted only in males of MD&HD and not in females.
Clin Chem: on both days 35&90 the following were noted: decr in serum electrolyte levels (K, Na, Cl) in MD&HD (2-15% of cont), decr in cholesterol in both sexes (22-59% of cont) and decr in TG of HD (40-56% of cont), incr in ALP level in HD (43-72% of cont) and, a small decr in total protein and alb was seen in all MD male & female rats.
Organ wt.: there were sporadic, not dose-dependent, changes in absolute and/or rel wt of thymus, brain, and heart; these changes were considered non-drug related. The following changes were considered drug related: incr in absol and rel wt of the **adrenal glands** in HDm, rel wt in MDm, and absol wt in the 1 surviving female rat; incr rel wt of the **lungs** in MD rats and incr in the absol wt in the single surviving female of HD; incr in absol and rel wt of the **liver** in HDm (36&54% respectively), a dose-related incr in rel liver wt was seen in all treated grs, both absol and rel wt of the liver was incr dose-dependently in treated females (reaching statistical sig only in MD&HD); **kidney** absol and rel wt was incr dose-dependently in males and the absol wt was incr in the only survivng HDf; the rel wt of the **spleen** was incr in MD&HDm, rel wt was incr in MDf and. and both absol and rel wt of the spleen was incr in the single surviving HDf; and the rel wt of the **testes** was incr in HD.
Gross and Histopath: there were no gross findings in any gr. Stress-related histopath findings were seen in rats that were found dead (3LD, 2MDm, 9HDf); such changes included: myocarditis (slight and focal), myocardial necrosis, congestion/edema of lungs, lymphoid necrosis of thymus and lymphoid depletion in spleen; none of these findings were seen in rats killed at end of study. In scheduled sacrifice rats. slight to moderate hypertrophy of centrolobular hepatocytes was observed in all HDm and the
single HDf. Electron microscopic exam revealed slight to moderate proliferation of smooth ER of centrolobular hepatocytes of HD.

Rat 3mo gavage (Cont.)

TK: Tables below from the sponsor for the parent and metabolite.

CL 284,846 (Parent)

Dose (mg/kg)	Sex	Day 0 Cmax (µg/mL)	Day 0 tmax (hr)	Day 0 AUC 0->24 (µg*hr/mL)	Day 28/29 Cmax (µg/mL)	Day 28/29 tmax (hr)	Day 28/29 AUC 0->24 (µg*hr/mL)	Day 91/92 Cmax (µg/mL)	Day 91/92 tmax (hr)	Day 91/92 AUC 0->24 (µg*hr/mL)
5	Male	0.7	1	2.06	0.8	2	1.9	1.3	1	4.13
	Female	0.9	1	1.67	0.7	2	1.5	1.3	2	3.01
50	Male	6.8	1	53.0	10.0	2	45.2	8.9	2	35.2
	Female	9.7	1	72.3	10.6	2	61.8	9.1	2	38.9
100	Male	11.5	2	90.4	13.4	2	76.7	12.9	2	68.3
	Female	16.2	2	124.5	13.9	2	100.9	11.1	2	82.1
200	Male	17.6	1	167.7	10.3	4	82.1	13.2	8	131.0
	Female	18.7	2	220.1	16.0	2	166.8	30.1	2	193.6

CL 284,859 (Metabolite)

Dose (mg/kg)	Sex	Day 0 Cmax (µg/mL)	Day 0 tmax (hr)	Day 0 AUC 0->24 (µg*hr/mL)	Day 28/29 Cmax (µg/mL)	Day 28/29 tmax (hr)	Day 28/29 AUC 0->24 (µg*hr/mL)	Day 91/92 Cmax (µg/mL)	Day 91/92 tmax (hr)	Day 91/92 AUC 0->24 (µg*hr/mL)
5	Male	0.4	1	1.42	0.8	2	2.56	1.2	2	5.15
	Female	0.4	1	0.92	0.4	2	1.13	0.8	2	2.24
50	Male	7.8	4	79.5	10.4	4	84.2	11.2	4	102.8
	Female	5.6	4	52.9	9.4	4	66.6	10.2	2	53.5
100	Male	11.9	2	140.1	17.7	4	154.4	15.0	2	152.5
	Female	7.5	8	92.8	12.7	4	122.4	10.0	4	109.4
200	Male	15.4	4	290.8	18.2	2	209.7	23.6	2	315.7
	Female	12.0	8	171.2	15.6	2	205.2	32.5	2	258.6

[a]Calculated from mean (n=3) plasma concentrations. Day 28/29 values for 100 mg/kg males and females and 200 mg/kg females were calculated from smaller population, due to mortalities. Day 91/92 values for 5 mg/kg females, 50 mg/kg females, 100 mg/kg males and females and 200 mg/kg males and females calculated from smaller population, due to mortalities.

Rat 3mo Gavage Tox Study (Cont.)

The data show conc incr with incr in dose and the incr in both conc and exposure was sub-linear. There seem to be no drug accumulation with time. There was sex difference with females having higher parent and lower metabolite conc than the males which is consistent with sex-dependent oxidative metabolism in the rat liver. Max conc was achieved within 1-2hr for the parent and 1-8hr for the metabolite.

The following are mean C_{max} values (ug/ml)±s.d for the parent at end of study d91/92:

Dose	m	f
5	1.3±0.4	1.3±0.1
50	10±3	11±5
100	13±4	16±3
200	18±2.3	30*

* only 2 rats/time point; inadequate no. to calculate s.d.

Summary & Conclusions:

Oral gavage administration of Zaleplon to male and female rats daily for 3months caused death in 9/10 females dosed 200mg/kg/d during the 1st few days of dosing. There were 3 deaths in the low dose of 5mg/kg and 2 deaths (males) in mid dose of 50mg/kg, these deaths were considered non-drug related because no histopath findings were seen in these rats and, the death in MD males was not dose related in addition to absence of any histopath. Clinical signs in all treated rats included: ataxia, hypoactivity, and prostration. convulsions during dosing noted in HD at 7wks during dosing. Mean wt gain was sig decr in HDm and in low and mid dose females; no drug effect on food intake. Serum ALP was moderately incr in HD. Drug related effect was seen on the wt of the liver (incr), adrenal gland (incr). spleen, kidney (incr), lung (incr), and, testes (incr). No gross findings and the only histopath was centrolobular hypertrophy in HD. Electron microscopic exam showed an incr in SER of the liver hepatocyte of HD rats. Mean max plasma conc (ug/ml) in males were 0.7±0.14, 6.8±2.4, 11.4±1.0, and 17.6±2.26 and in females: 0.9±0.2, 10±1.8, 16.2±3.0, and 18.7±4.0 for the 5, 50, 100, and 200mg/kg/d doses respectively. There seem to be no drug accumulation and conc and exposure incr sub-linear with dose. The **NOEL** in this study is **<5mg/kg/d** because of decr in wt gain observed in females dosed 5mg/kg/d and changes in some organ wts in animals of this gr.

3 month oral **gavage** study with 1 month recovery (# 26170/Lederele & 27696/Japan)
Study Issue Date: Mar 1994 Lab: [redacted]

Doses: **3, 10, 30, 100mg/kg/d**; control received the vehicle: carrier*/polysorbate.
Strain/No./Sex/Dose: Sprague Dawley/15/sex/dose. 10/sex/dose were killed at end of 3mo and the remaining 5/sex/dose were used for the 1mo recovery.
Parameters assessed: mortality, clinical signs, B.wt/wt gain, food intake, ophthalmology, hematology, clin chem, urinalysis, water intake and urine volume, organ wts, gross exam, and histopath of all organs/tissues. Bone marrow smears were evaluated from 5/sex at end of study and from cont and HD at end of recovery. Electron microscopy for liver & kidneys was done on all rats in cont and HD only.

* carrier consisted of methocel which is methyl cellulose 0.5% and Tween 80 at 0.1% in water.

Results:
Mortality & Clinical Signs: drug related deaths were as follows:

3mg/kg	1/15f study day 17
30mg/kg	2/15f study days 41&49
100mg/kg	1/15f study day 0 (after 1st dose)
cont	1/15m study day 45;

Non drug related - accidental gavage errors were seen in: 1/15 HDm study day 81; cont 1/sex days 45&75. The 1 of the 2 females dosed 30mg/kg showed signs of cyanosis, apnea, and incr body tone, however, no grave signs were seen in the other dosed females.

Clinical signs included abnormal gait and decr in muscle tone seen in almost all rats dosed ≥10mg/kg/d and several rats dosed 3mg/kg/d, the frequency of these signs incr with incr in dose. In addition to these signs, the following noted in rats dosed 30&100mg/kg/d: salivation, flush, convulsions (1mo postdose), inactivity, abnormal posture, incr in body tone, loss of righting reflex, running!, and tail elevation. During recovery period, all these signs disappeared except 1m in HD was salivating and another m in this gr had a slight incr in body tone.
B.wt/Food Intake: mean B.wt was sig decr ($p<0.05$ or 0.01), during the periods: 7-35, 7-49, 7-49, and 7-70 in males dosed 3, 10, 30, and 100mg/kg/d respectively, these decreases were 3-6%, 6-10%, 5-8%, and 7-9% lower than the corresponding vehicle cont respectively. Mean B.wt in HDf was sig incr during days 28-90 (6-12% over the cont). During recovery period, mean B.wt in males were comparable between drug grs and cont. In HDf during recovery, gained more wt than the cont (10-14% over the cont). No drug effect on mean wt gain in females. There were inconsistent changes in food intake, a sig incr (13%) in HDm during the periods 49-70 & 77-90 and in all female drug grs on specific days. However, a sig decr in food intake occurred in males dosed 10mg/kg and 21% decr in wt of HDm recorded during recovery days 0-7 rel to the cont.

These changes in food intake ranged between 7-13% decr in males and in 5-42% in females, rel to the corresponding cont. values.

Ophthalmology, Urinalysis, & Urine volume/water intake: no drug effect on any of these parameters except for random increases in urine volume and water intake that were not-dose dependent and not seen in both sexes. During recovery period sig incr in water intake was seen in females dosed 100mg/kg but no effects in males.

Hematology: no clear drug related effects were noted in any parameter. The following reached statistical sig: HcT incr 5&6.7% over the cont in MD&HDm and MCHC decr 2&5% in MD&HDm; at end of recovery, HcT was still elevated but now in males dosed 10&30mg/kg and not 100mg/kg (5.5&10% respectively). In females dosed 100mg/kg, WBC count was sig incr (35% of cont), RBC count decr 5%, MCV incr 7% (also in MD incr 2.5% over cont), MCH incr 5%, and MCHC decr 4%. During recovery period all these effects in HD were comparable tot he cont and few changes seen in MD females that reached sig level.

Clin Chem: any changes were comparable to cont values at end of recovery. The following effects were seen in HD males: incr in Alb (4.4%), incr in Ca (6.7%; also incr in MD at 11% of cont), incr in inorganic P (14%, also in MD 19% of cont), incr in Cl (2%), K seems to have an increasing trend but not dose dependent and sig only at 3&30mg/kg dose (30&26% respectively). In HD females at end of study: ALP level was sig incr (51% of cont), urinary nitrogen decr (14%), inorganic P incr 17% (with a trend in the lower doses towards an incr, though statistical sig was not reached and the incr not dose dependent), incr in K (25%), and decr in Cl (5%).

Organ wt.:

Adrenals: absol & rel wt in 30&100mg/kg dosed **males** were sig and dose-dependently incr (22&41% absol; 26&48% of cont; also incr in 10mg/kg dose at 11%). In **females** absol & rel wt incr in HD only at 56% absol; 39% rel)

Liver: absol & rel wt incr in both sexes with the rel wt incr dose-dependently in all dose grs of both sexes; no effect at end of recovery except for some changes in absol wt in females but this may have been due to the sig incr in mean B.wt in females of HD. The incr in liver wt ranged between 17-64% for absol wt for both sexes and 10-45% for rel wt in both sexes.

Kidney: absol wt incr 10% HDm and 28% HDf. Rel wt incr in all 4 male dose grs (7-15%) non-dose dependently and only in HDf (11%).

Spleen: absol (only males) and rel wt of HD rats incr (17&22.5% respectively for m; 21% rel wt in Hdf).

Gross and Histopath: the following organs/tissues were enlarged: liver, adrenals, and spleen; no other sig gross findings. At end of dosing, **centrilobular hypertrophy of hepatocytes** was seen in 1/10, 3/10, and 5/10 males dosed 3, 30, and 100mg/kg/d and in females 2/10, 2/10, 3/9, and 4/9 dosed 3. 10, 30, and 100mg/kg/d respectively. Incr in **extramedullary hematopoeisis** in 2/9 HDf, hypertrophy of zona fasiculata in the

adrenals in 1/10 & 4/10 males dosed 30&100mg/kg respectively, and in 3/9 7/9 females dosed 30&100mg/kg/d respectively. **Brown pigment disposition in spleen** seen in 1/10, 1/10, 4/10, & 10/10males dosed 3, 10, 30, and 100mg/kg. At end of recovery period, the only drug finding was the brown pigment in the spleen noted in 2/4 HDm and in 3/4, 4/4, and 5/5 females dosed 3, 30, and 100mg/kg/d. Em showed an incr in SER of hepatocytes in HD rats; a finding not seen at end of recovery.

Summary & Conclusions:

Oral gavage administration of CL 284-846 to male and female rats at 3, 10, 30, or 100mg/kg/d for 30 days caused death in 2 females dosed 30mg/kg and 1 female dosed 200mg/kg. Clinical signs included abnormal gait and decr in muscle tone seen in almost all rats dosed ≥10mg/kg/d and several rats dosed 3mg/kg/d, the frequency of these signs incr with incr in dose. Also, the following noted in rats dosed 30&100mg/kg/d: salivation, flush, convulsions (1mo postdose), inactivity, abnormal posture, incr in body tone, loss of righting reflex, running!, and tail elevation. During recovery period, all these signs disappeared except 1m in HD was salivating and another m in this gr had a slight incr in body tone. Mean B.wt was sig decr in males and incr in females; i.e. a sex difference was observed. During recovery period, mean B.wt was comparable in males but slightly more in females ($p<0.05$). There were inconsistent changes in food intake, a sig incr in HDm and in all female drug grs on specific days, but a sig decr in food intake in males dosed 10mg/kg and 21% decr in wt of HDm during recovery days 0-7 rel to the cont. These changes ranged between 7-13% decr in males and in 5-42% in females, rel to the corresponding cont. values. Ophthalmology, Urinalysis, & Urine volume/water intake, generally, no drug effect on any of these parameters except for random increases in urine volume and water intake that were not-dose dependent and not seen in both sexes. Hematology, no clear drug related effects were noted in any parameter some values reached statistical sig. HcT level incr 5&6.7% over the cont in MD&HDm and at end of recovery, HcT was still elevated but now in males dosed 10&30mg/kg and not 100mg/kg (5.5&10% respectively). Clin Chem generally no drug effect and any changes were comparable to cont values at end of recovery. In HD females at end of study, ALP level was sig incr (51% of cont). A sig incr in absol and rel wt of the following organs were seen: **Adrenals** (males in 30&100mg/kg 22&41% absol; 26&48% rel of cont; females incr in HD only at 56% absol; 39% rel); **liver** (the rel wt incr dose-dependently in all dose grs of both sexes; 17-64% for absol wt for both sexes and 10-45% for rel wt in both sexes); **Kidney** (10% HDm and 28% HDf, Rel wt incr in all 4 male dose grs 7-15%, non-dose dependently and only in HDf 11%); **spleen** (rel wt of HD rats incr 22.5% respectively for m; 21% rel wt in Hdf). Gross exam showed enlargement of

the liver, adrenals, and spleen; no other sig gross findings. At end of dosing, **centrilobular hypertrophy of hepatocytes** was seen in males dosed 3, 30, and 100mg/kg/d and in females dosed 3, 10, 30, and 100mg/kg/d. Incr in **extramedullary hematopoeisis** in HDf, **hypertrophy of zona fasiculata** in the adrenals in males dosed 30&100mg/kg and, in females dosed 30&100mg/kg/d. **Brown pigment disposition in spleen** seen in all male grs including all 10/10 dosed 100mg/kg. At end of recovery period, the only drug finding was the brown pigment in the spleen noted in 2/4 HDm and in 3/4, 4/4, and 5/5 females dosed 3, 30, and 100mg/kg/d. Em showed an incr in SER of hepatocytes in HD rats; a finding not seen at end of recovery. The **NOEL** in this study could not be determined due to histopath in the 3mg/kg/d therefore, it can be assumed it is **<3mg/kg**

3 month oral **gavage** tox study in rats (# 89343/89344)
Study Initiation Date: Dec 1989 Lab: [redacted]

Dose: **single dose of 100mg/kg/d***; control received the vehicle: carrier**/polysorbate.
Strain/No./Sex/Dose: Sprague Dawley/10/sex/dose. 15/sex/dose for TK, these rats were for blood collection only and were killed without necropsy at end of study***
Parameters assessed: mortality, clinical signs, B.wt/wt gain, food intake, ophthalmology, hematology, clin chem, urinalysis, TK, organ wts (not done for animals found dead or killed in moribund), gross exam, and histopath of all organs/tissues. Bone marrow smears were done but not examined. Electron microscopy processing without further analysis, for liver was done on 3/sex/gr at sacrifice.

* this dose was selected because high mortality was seen in rats dosed 200mg/kg within 1wk of oral dosing.
** carrier consisted of methocel which is methyl cellulose 0.5% and Tween 80 at 0.1% in water.
*** It is unclear whether these are the same rats used in the previous 3mo rat tox study# 89324. The data provided in the 2 studies are the same.

Results:
Mortality & Clinical Signs: death occurred on day1 of dosing in 1 each m&f dosed 100mg/kg and a total of 4 deaths in cont (3f d69 and 1m d44). These cont rats were inadvertantly administered a single dose of 100mg/kg. Clinical signs included general CNS depression (prostration, hypoactivity, & ataxia). Convulsions were seen upon handling during dosing in 1m & 2f after 6wks of dosing. Also, stained peri-anal area and lacrimation were seen in females.
B.wt & Food Intake: mean wt was sig decr in males within 2-4wk (6-12% less than cont) and remained low till end of study (rel to the cont). No effect in females. Mean wt

3mo oral gavage - single dose (Cont.)

gain was sig decr in both sexes starting from the 2nd wk (30% less than cont) through d34 at 70% less than the cont. A loss of -16% rel to cont in females noted during days41-48 however, in the following period (d48-55) the females showed 1222% rel to cont values. On days 69-76, females showed loss of -547% rel to cont whereas, mean wt of males at this period was 265% of cont. The s.d. was very high in some of the readings. No drug effect on food intake; the increases noted were caused by food wastage where drug rats partially ate the pellets and these were dropped from the cage and the animals did not have the chance to finish them.
Ophthalmology: focal illumination and indirect ophthalmoscopy. No drug effect.
Hematology: RBC count was sig decr at end of study in both sexes (5-6% of cont), an incr noted in MCV (5.5&7.6%) in males at mid and end of study, WBC count was incr in males mid study (30%) and end of study (70%) and females had a 35% incr only at end of study.
Clin Chem: sig decr noted in serum electrolytes (Na, K, Cl)(1-13%) in both sexes, incr in P_i, decr in total proteins & Alb on both sampling times in females only (mid and end of study; 6-8% of cont).
TK: after 1st dose, mean C_{max} for the parent was 11.5ug/ml (AUC_{0-24hr} 90ug.hr/ml) in m and 16ug/ml in f (AUC_{0-24hr} 125ug.hr/ml), conc were higher in f than m. There seemed to be no drug accumulation with time (mean C_{max} at end of study for m&f were 13&11ug/ml respectively).
Organ wt: sig incr in absol and rel wt of the adrenals, liver, and kidneys in both sexes.
Gross and Histopath: no findings in either dead or scheduled sacrifice rats.

Summary and Conclusions:

Oral gavage administration of CL 284-846 to rats for 30d at 100mg/kg caused death after a single administration also, 4 cont rats that were inadvertantly given a single dose of the drug also were found dead. Clinical signs were those of CNS depression and convulsions upon handling at about 6wk postdose. Mean wt gain was sig decr in males; no effect on food intake in either sex. Hematology findings included decr in RBC, incr in WBC. Changes in clin chem included decreases in serum Na. Cl. and K. Mean absol and rel wt of the liver, kidneys, and adrenals were sig incr in both sexes. These increases in organ wts were not accompanied by any histopath findings. Mean C_{max} in males was 11.5ug/ml and 16ug/ml in f.

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MOUSE

Mouse 3 month oral **dietary** study **(# 386)**
Study Initiation Date: Apr 1991 Lab: [redacted]

Doses: **1, 5, 40, 240, or 1500mg/kg/d**; control received the diet alone.
Strain/No./Sex/Dose: CD-1/10/sex/dose; additional 60/sex in dose grs 1, 40, and 240mg/kg/d were used for TK; 6/sex/dose were bled on days 7&90 from the retro-orbital sinus at 0, 4, 8, 12, and 18hr after the start of the dark cycle. The 0hr sample was also used as the 24hr sample for the previous day.

Parameters assessed: mortality, clinical signs, B.wt/wt gain, food intake, organ wts/only the liver, complete gross exam, and histopath of all scheduled sacrifice and dead.

Results:
Mortality & Clinical Signs: 1m & 1f dosed 1500mg/kg were found dead on days 53&61 the female showed muscular contractions for 20sec on its way to be weighed. A 2nd female in this gr was killed in moribund on d60 with no signs of motility, crouched posture, and dyspnea 4days prior to sacrifice. The only clinical sign was an intense yellow discolored urine.
B.wt, Food Intake: females showed dose-related incr in wt gain (doses 40, 240, & 1500mg/kg); the incr was 13% over cont in HD. This incr was not accompanied by incr in food intake but a small and sig decr noted in food intake; 11% less than cont. Consequently, food efficiency (wt gain/food consumption) was sig incr in these mice (1.72 in HD vs. 0.88cont in females). A non-dose dependent incr in wt gain and food efficinecy was also seen in males but the incr was smaller than that in f.
Liver wt: dose-related incr in absol and rel wt in females dosed ≥40mg/kg (absol. 13-88% over cont; rel: 9-57% over cont) and in males dosed 240&1500mg/kg (absol. 14&43% respectively, rel.: 11&39% over the cont, respectively).
Gross & Histopath.: no gross findings except in HD where the liver was enlarged in 1m and dark brownish discoloration in 8/9m and 2/8f dosed 1500mg/kg/d. Moderate to severe (8/9m) and slight to moderate (9/9f) centrolobular hypertrophy of hepatocytes was seen in all mice dosed 1500mg/kg. Centrolobular hypertrophy of the hepatocytes was also seen in 2/20 mice dosed 240mg/kg. "Hydropic degeneration" in 3males dosed 240mg/kg was reported; **the reviewer is unclear what this means toxicologically or pathologically**. "Massive and sub-massive" necrosis was reported in 1f each in 240 and 1500mg/kg grs; **again, the reviewer is unclear what this means.** The sponsor considered these findings to be idiosyncratic.

Mouse 3mo oral dietary (Cont.)

TK: there seemed to be no drug accumulation after repeate dosing and no enz induction. Females seemed to have *lower* conc and exposure than males at the same doses; a finding opposite to that seen in rats. No parent or its main metabolite were detectable at the 1mg/kg dose at any time (ql=5ng/ml). Tables below from sponsor:

Pharmacokinetics in Mice Following Oral (Diet) Dosing of CL 284,846 (Sedative/Hypnotic) for Three Months

CL 284,846 (Parent)

		Day 7				Week 13		
Dose* (mg/kg/day)	Sex	C_{max} (µg/mL)	T_{max} (hr)	AUC 0->24 (µg.hr/mL)	Dose* (mg/kg/day)	C_{max} (µg/mL)	T_{max} (hr)	AUC 0->24 (µg.hr/mL)
1 (1.00)	Male	0.11	24	1.96	1 (0.93)	0.03	12	ND
1 (0.94)	Female	0.04	24	0.78	1 (1.05)	0.05	12	ND
40 (42.1)	Male	0.18	4-8	2.83	40 (37.0)	0.07	8	1.23
40 (41.8)	Female	0.12	8	1.60	40 (39.0)	0.07	16	0.88
240 (221)	Male	0.40	24	5.84	240 (222)	0.79	12	9.45
240 (253)	Female	0.24	4	3.30	240 (237)	0.16	4	3.08

CL 284,859 (Metabolite)

		Day 7				Week 13		
Dose* (mg/kg/day)	Sex	Cmax (µg/mL)	Tmax (hr)	AUC 0->24 (µg.hr/mL)	Dose* (mg/kg/day)	Cmax (µg/mL)	Tmax (hr)	AUC 0->24 (µg.hr/mL)
1 (1.00)	Male	<0.005	ND	ND	1 (0.93)	<0.005	ND	ND
1 (0.94)	Female	ND	ND	ND	1 (1.05)	<0.005	ND	ND
40 (42.1)	Male	0.08	8	0.95	40 (37.0)	0.04	8	0.62
40 (41.8)	Female	0.04	16	0.48	40 (39.0)	0.05	16	0.69
240 (221)	Male	0.96	24	11.86	240 (222)	1.05	8	8.44
240 (253)	Female	0.63	4	7.83	240 (237)	0.84	8	10.38

ND = Not determinable
Calculated from mean (n=6 mice/timepoint/sex) plasma concentrations.
*Values in parentheses are the actual dose of CL 284,846 based on food consumption.
C_{max} = Maximum Drug Concentration
T_{max} = Time to reach C_{max}
AUC = Area under the plasma concentration time curve
Quantitation Limit = 0.005 µg/mL

Conc and exposure incr non-linearly with increasing dose, the incr was sub-linear. Mean C_{max} took 4-24hr to reach for the parent and its metabolite. Conc and exposure at 1&40mg/kg in both sexes for the parent and metabolite were lower on wk 13 than the corresponding values on d7.

Mouse 3mo dietary (Cont.)

Summary & Conclusions:

Oral dietary administration of CL 284-846 to mice at 1, 5, 40, 240, or 1500mg/kg/d for 3mo caused death at HD. Clinical signs were absent except for a yellow-colored urine. Incr in liver wt with centrolobular hypertrophy was seen in mice dosed ≥40mg/kg. Hydropic degeneration was also seen in these mice; the reviewer is unclear what these findings mean. **The NOEL in this study is 5mg/kg.**

Mouse 3 month oral **dietary** study (**# 438**)
Study Initiation Date: Aug 1993 Lab: [redacted]

Doses: **25, 50, 100, and 200mg/kg/d**; control received the diet alone.
Strain/No./Sex/Dose: C57BL/6NCrIBR 10/sex/dose; additional 48/sex/dose was used for TK study (no gross or histopath in this gr). Blood was collected from the retro-orbital sinus of 4mice/sex/dose/time point on d7&wk13 and after each bleeding, the mouse was killed.

Parameters assessed: mortality, clinical signs, B.wt/wt gain, food intake, TK, organ wts, complete gross exam, and histopath of all scheduled sacrifice and dead mice.

Results:
Mortality & Clinical Signs: total of 7 mice found dead: 1m cont, 2m&1f 25mg/kg, and 3m dosed 50mg/kg. Death occurred between days 11-80 of dosing. No drug related clinical signs in any gr. The cause of death was not stated, from the individual animal record, histopath findings in the 3 males dosed 50mg/kg showed lymphoid depletion of the thymus in 2/3 mice and bone marrow hyperplasia in 1/3, and the 3rd mouse showed stomach focal erosion. It seems that the death in these mice may not have been drug related.
B.wt & Food Intake: in treated male mice, there were no drug effects on mean wt or wt gain except for some random changes noted throughout the study. Females of all drug grs except the 50mg/kg showed a trend towards incr in mean wt and wt gain throughout the study that reached statistical sig. at doses ≥100mg/kg (20&21% over cont for wt gain and 8% over the cont for mean wt). Mean food intake in HDf was higher (6% over cont) than the cont except it was lower than the cont on study d3. Mean food values of other drug grs was comparable to the cont. No drug effect on food efficiency in any sex or gr.
Organ wt: no drug effect except for a small but statistically sig decr in absol and rel wt of the spleen in males dosed 100&200mg/kg (absol. 17&17.5%; rel 17&20% respectively; compared with the corresponding cont values).

Mouse 3mo dietary (Cont.)

Gross & Histopath: no gross or histopath findings that were drug related in either the mice that were found dead or those killed at scheduled sacrifice.
TK: plasma drug level incr (non-linearly), with incr dose. There seemed to be no drug accumulation with repeate dosing, and no sex difference in conc or exposure in either the parent or its metabolite.

Parent:

Dose (mg/kg)	Sex	Conc (ug/ml) d7	Conc (ug/ml) wk13	AUC_{0-24}(ug.hr/ml) d7	AUC_{0-24}(ug.hr/ml) wk13
25	m	0.54±0.26	0.10±0.06	2.2	1.5
	f	0.08±0.05	0.10±0.05	1.2	1.0
50	m	0.17±0.20	0.20±0.03	2.5	2.1
	f	0.27±0.36	0.10±0.04	1.7	1.3
100	m	0.50±0.20	0.32±0.14	5.7	3.6
	f	0.21±0.20	0.22±0.10	3.1	2.6
200	m	1.73±1.30	0.65±0.45	18	7.1
	f	1.12±1.11	0.85±0.66	11	8.2

Mean T_{max} was reached between 0-8hr in all grs except it was 12hr in males dosed 25mg/kg for 13wk. Mean plasma conc for the metabolite (CL 284,859) ranged between 0.01±0.01 to 0.76±0.53ug/ml and mean AUC_{0-24hr} ranged between 0.93-6ug.hr/ml, mean T_{max} ranged between 4-12hr and 18hr during wk13 in females dosed 25mg/kg.

Summary & Conclusions:
Oral dietary administration of CL-284,846 to male and female C57BL/6NCrlBR mice caused death in 6 mice (2m&1f 25mg/kg and 3m dosed 50mg/kg). Death occurred between days 11-80 of dosing. The cause of death was not stated, from the individual animal records, the histopath findings did not reveal any clear cause of death. There were no clin signs in any gr. No drug effect on mean wt/wt gain in males and an increasing trend in mean wt gain was seen in f except in f dosed 50mg/kg. No drug effect on food intake except for an incr in HDf. No drug effect on organ wts except for a decr in mean absol and rel wt of the spleen in males dosed 100&200mg/kg. No gross or histopath findings in any gr. Mean C_{max} ranged between 0.08-1.7ug/ml and exposure from 1-18ug.hr/ml for the parent and mean C_{max} for the main metabolite, CL 284,859, ranged between 0.01-0.76ug/ml and mean exposure were 1-6ug.hr/ml. Mean T_{max} was reached between 0-12hr for the parent and 4-18hr for the metabolite. **The NOEL is <25mg/kg/d** due to death in this gr, though no mice died at higher doses (100 & 200mg/kg). The cause of deaths in this gr and the 50mg kg could not be verified.

Mouse 5 month oral **gavage** study (# 427)
Study Initiation Date: Mar 1993 Lab: [redacted]

Doses: **0, 20, 40, 80, 160, and 240mg/kg/d**; dosing volume was 10ml/kg; control received the vehicle cont which was methylcellulose (0.5%) anf Tween 80 (0.1%).
Strain/No./Sex/Dose: CD-1 (ICR)BR 15/sex/dose; additional 8/sex/dose were used for TK study (with 12/sex/dose as backup for TK). Blood was collected from the retro-orbital sinus of 4mice/sex/dose/time point on d0&3mo upto 24hr postdose. After each bleeding, the mouse was killed. A single female assigned to the TK section and dosed 240mg/kg, was found dead on d0 6hr postdose*. This f was not examined postmortem. Gross or histopath was not done on the TK mice killed on d0, however, gross exam and organ wts were done on TK mice at the 3mo sampling time. Animals that were found dead had only gross exam and were discarded.

Parameters assessed: mortality, clinical signs, B.wt/wt gain, food intake/efficinecy, TK, organ wts (only from the TK mice, for the tox mice, only the liver was weighed), only the liver was grossly examined and preserved in 10% phosphate buffered formalin but no histopath exam was done.

Results:
Mortality: there was a total of 19m and 18f deaths as follows (Tox+ TK sections):

20mg/kg/d	3m; 3f
40mg/kg	0m; 3f
80mg/kg	6m; 1f
160mg/kg	3m; 1f
240mg/kg	7m; 10f*

* 3m & 9f of 240mg/kg gr were found dead on d2 or 3 of study.

In addition to the above drug related deaths, the following deaths were contributed to gavage error: 2m cont, 3m 20mg/kg, 1/sex 40mg/kg, 1m/2f 80mg/kg, 1/sex 160mg/kg, and 2m 240mg/kg. Cause of death in the other animals was not identified.

Clinical Signs: initial hyperactivity and gait in all drug grs, severity being dose-dependent. Dose-dependent decr in motility in mice dosed ≥80mg/kg/d, prostration seen in mice dosed 160&240mg/kg (at the 240mg/kg, prostration was more frequent and associated with dyspnea). Onset of signs occurred shortly after dosing and lasted 3hr postdose. Clinical signs occurred from day0 and continued throughout the study period.
B. Wt, Food Intake: mean wt gain was decr in m dosed ≥20mg/kg rel to the cont reaching statistical sig for the 240mg/kg on 3rd wk of study, wk4 for the 160mg/kg, and wk5 for doses ≤80mg/kg. No drug related wt gain change in f. Food intake was slightly

Mouse 5mo oral gavage (Cont.)

decr in both sexes at ≥20mg/kg at the start of the study (1st few wks). No drug effect on food efficiency in f but a decr seen in all m grs reaching statistical sig at ≥ 40mg/kg.
Organ wt: in the 10/sex/dose mice from the TK section that had complete necropsy, a sig and dose-dependent incr in absol and rel wt of the liver was seen in m dosed ≥160mg/kg/d; a small and not sig incr noted in f dosed 240mg/kg. In mice assigned to the Tox section, only the liver was weighed and no drug effect was seen in any gr.
Gross & Histopath: no drug related gross findings in any mouse in the TK or Tox sections except for pale kidneys with or without rough surface.
Histopath exam of the TK mice was done only on the liver, GI, and any gross lesions in the 10/sex/dose. Minimal to slight hepatocellular centrolobular hypertrophy was seen in 1/sex 80mg/kg, 5/10m 160mg/kg, 7/10m/1/10f 240mg/kg. Foci of hepatocellular necrosis was seen in 1/10m/3/10f dosed 20mg/kg, 1/sex 40mg/kg, and 1/sex 80mg/kg. These findings were considered not drug related due to the incidence and distribution. No histopath done on any animals that were found dead in the TK section except for the 1f dosed 20mg/kg where the subcutaneous mass was shown to be an osteosarcoma. No histopath was done on any of the tox mice except those that were found dead. Hepatocellular focal necrosis seen 1/sex 20mg/kg gr, 2m/1f 160mg/kg, and 1m 240mg/kg. One f dosed 160mg/kg showed severe glomerlulonephritis, and 1m 240mg/kg and 1f 40mg/kg had erosion of the gastric mucosa.
TK: below are means±s.d. for max conc and mean exposure (no s.d. values provided). The T_{max} was 0.5-1hr for both the parent and metabolite (CL 284-859; the desethyl).

PARENT:

Dose (mg/kg)	Sex	C_{max} (ug/ml) d0	C_{max} (ug/ml) 3mo	AUC_{0-24}(ug.hr/ml) d0	AUC_{0-24}(ug.hr/ml) 3mo
20	m	1±0.34	4±2	1	4
	f	1±0.42	2.6±1.7	1.2	2.2
40	m	4±3.2	6.4±3	4	7
	f	4.4±1	9±1	5	6
80	m	11±0.72	20±5	13	21
	f	10±1.3	15±4	14	16
160	m	19±9	30±4	40	37
	f	24±12	35±7.5	34	39
240	m	24±3.5	31±7	58	54
	f	30±11	33±6	91	52

Mouse 5mo oral gavage (Cont.)

METABOLITE:

Dose (mg/kg)	Sex	Conc (ug/ml) d0	Conc (ug/ml) 3mo	AUC_{0-24}(ug.hr/ml) d0	AUC_{0-24}(ug.hr/ml) 3mo
20	m	1±0.2	2±0.6	1	2.2
	f	1.4±0.4	1.6±0.5	1.3	2
40	m	2±1	3±1	2	3.4
	f	3.4±0.4	4±1	5	5
80	m	3.3±0.4	5±4	6	9
	f	7±1	6.5±1.6	12	10
160	m	12±1.6	8±1.3	22	20
	f	9±2	12±1.6	24	22
240	m	8±4	8±1	25	28
	f	17±6	11±2.7	62	25

There seem to be no sex difference in conc and exposure though sometimes the values tended to be higher in f than those in m. The conc and exposure incr with dose, the incr was not linear for both the parent and metabolite. Generally, there seem to be no drug accumulation with time.

Summary & Conclusions:
Oral gavage administration of CL 284,846 to CD-1 mice for 5mo at 20, 40, 80, 120, and 240mg/kg/d caused death in a total of 37 deaths in all dose grs; cause unknown. Clinical signs included dose-dependent initial hyperactivity and gait in all drug grs, dose-dependent decr in motility in mice dosed ≥80mg/kg/d, and prostration seen in mice dosed 160&240mg/kg (at the 240mg/kg, prostration was more frequent and associated with dyspnea). Onset of signs occurred shortly after dosing and lasted 3hr postdose. Clinical signs occurred from day0 and continued throughout the study period. Mean wt gain was decr in m dosed ≥20mg/kg rel to the cont reaching statistical sig for the 240mg/kg on 3rd wk of study, wk4 for the 160mg/kg, and wk5 for doses ≤80mg/kg. No drug related wt gain change in f. Food intake was slightly decr in both sexes at ≥20mg/kg at the start of the study. No drug effect on food efficiency in f but a decr seen in all m grs reaching statistical sig at ≥ 40mg/kg. In the mice designated to the TK section where complete necropsy was done, a sig and dose-dependent incr in absol and rel wt of the liver was seen in m dosed ≥160mg/kg/d; a small and not sig incr noted in f dosed 240mg/kg. In mice assigned to the Tox section, only the liver was weighed and no drug effect was seen in any gr. No drug related gross findings in any of the drug

Mouse 5mo oral gavage (Cont.)

grs. except for pale kidneys with or without rough surface. Histopath exam of the TK mice was done only on the liver, GI, and any gross lesions in the 10/sex/dose. Minimal to slight hepatocellular centrolobular hypertrophy was seen in 1/sex 80mg/kg, 5/10m 160mg/kg, 7/10m/1/10f 240mg/kg. Foci of hepatocellular necrosis was seen in 1/10m/3/10f dosed 20mg/kg, 1/sex 40mg/kg, and 1/sex 80mg/kg. These findings were considered not drug related due to the incidence and distribution. No histopath done on any animals that were found dead in the TK section except for the 1f dosed 20mg/kg where the subcutaneous mass was shown to be an osteosarcoma. No histopath was done on any of the tox mice except those that were found dead. Hepatocellular focal necrosis seen in 1/sex 20mg/kg gr, 2m/1f 160mg/kg, and 1m 240mg/kg. One f dosed 160mg/kg showed severe glomerlulonephritis, and 1m 240mg/kg and 1f 40mg/kg had erosion of the gastric mucosa. Mean max conc ranged between 1-35ug/ml for the parent and 1-17ug/ml for the metabolite, the corresponding exposure values were 1-91ug.hr/ml and 1-62ug.hr/ml, respectively. **A NOEL could not be determined in this study.**

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Conclusions for Dose Selection for the Mouse and Rat Carcinogenicity Studies:

Mouse:
Based on the above studies and the correspondances between the Division and the sponsor, the doses of zaleplon selected for the mouse dietary car study were: **m: 10, 40, 80mg/kg/d and f: 25, 100, 200mg/kg/d. However, the doses that were actually tested were: 25, 50, 100, & 200mg/kg/d for both sexes.** ***The reviewer could not find an explanation from the sponsor to explain this change in doses selected; it is only assumed that these doses will cover the dose range for both males and females.***

For the gavage car study, the doses were **1, 5, & 50mg/kg/d.**

Rat:
For the rat dietary car study the doses selected were: **1, 10, 20mg/kg/d.**

Summary table for TK data for the rat and mouse following **DIETARY** administration for 3mo (values are means±s.d.; no s.d. was reported for exposure):

Dose (mg/kg)		Mouse C_{max}	Mouse AUC_{0-24hr}	Dose (mg/kg)		Rat C_{max}	Rat AUC_{0-24hr}
25	m	0.54±0.3	2.2	1	m	0.01±0.01	0.4
	f	0.1±0.05	1.5		f	0.02±0	0.34
50	m	00.2±0.03	2.5	10	m	0.2±0.06	5
	f	0.3±0.4	1.7		f	0.3±0.02	5
100	m	0.5±0.2	5.7	100	m	4±0.5	56
	f	0.22±0.1	3		f	4±2.4	90
200	m	2±1	18				
	f	1±	11				

The mean T_{max} for both the rat and mouse ranged between 0-12hr.

Human mean C_{max} and AUC measured after a single administration of the maximum proposed clinical dose of 10mg/d were, 40±20ng/ml and 100±40ng.hr/ml respectively.

Summary table for TK data for the rat and mouse following **ORAL GAVAGE** administration for 3mo (values are means±s.d.; no s.d. was reported for exposure):

Dose (mg/kg)		Mouse C_{max}	Mouse $AUC_{0\text{-}24hr}$	Dose (mg/kg)		Rat C_{max}	Rat $AUC_{0\text{-}24hr}$
20	m	4±2	4	5	m	1.3±0.4	4
	f	3±1.7	2		f	1.3±0.1	3
40	m	6±3	7	50	m	10±3	53
	f	9±1	6		f	11±5	72
80	m	20±5	21	100	m	13±4	90
	f	15±4	16		f	16±3	125
160	m	30±4	40	200	m	18±2	168
	f	35±7.5	39		f	30*	220
240	m	31±7	58				
	f	33±6	91				

* only 2 rats/time point; inadequate to calculate s.d.

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Mouse Carcinogenicity Studies:

Dietary Administration: 2 year study (# 450; GTR# 29394)
Study Date: June 1994
Report Date: July 1997
Lab: [redacted]

Strain/# per sex/dose: CD-1; 75/sex/dose; (additional 4/sex were also dosed with the drug in case of deaths in the main 40 mice/sex; these mice were killed at 12mo); additional 40/sex/dose for TK; drug plasma levels were determined on d7 and 12mo of dosing, blood collected overnight at 7&11pm, 3&7am and 1pm (4mice/sex/dose/time point were used).

Doses (mg/kg/d)/duration: 0, 0, 25, 50, 100, 200 for 104 wks; Two cont grs were used and they recieved the diet without the drug.

Doses were selected based on 2wk and 3m dietary dose range finder studies. Death occurred at 1500mg/kg/d in the 3mo study and hepatic histopath was seen at ≥240mg/kg in the 2wk study. Therefore, the HD for the car study is 200mg/kg.

Parameters assessed: mortality, clinical signs, B.wt, food intake, ophthalmology, hematology (12&24months from retro-orbital sinus), TK, gross exam, and, histopath of approximately 50 tissues per mouse (all moribund, found dead, or scheduled mice were examined).

Results:
Mortality & Clinical Signs: statistics was done using log rank (for difference in survival among grs), trend analysis with ordinal and dose proportional scaling (for dose-response assessment), pair-wise comparisons between the 100 & 200mg/kg dose grs and the combined cont, was also done, and 2-tailed test was done in each case. Separate analysis was done for each sex.

There was a sig. dose- and drug-related incr in mortality in both sexes with more deaths in f than m. In males and females a sig trend in increased mortality was seen across the grs (p=0.04m & 0.004f on dose scale and 0.07m & 0.005f on ordinal scale). When the HD of 200mg/kg gr was excluded from analysis, a decreased trend of survival was not seen in males but a marginal decr was seen in f across the other dose grs (p=0.05). Both in m and f of 200mg/kg, a statistically sig decr in survival was seen using pairwise comparisons with small but sig decr in f dosed 100mg/kg (but not m). It was stated by the sponsor that these deaths were not related to adverse clinical signs, marked changes in B.wt/food intake, or other drug related effects.

Mouse dietary 2yr car (Cont.)

Table below from the sponsor presents death rates:

	DOSAGE (mg/kg/day)				
	0	25	50	100	200
MALE					
Animals initially on study	150	75	75	75	75
Accidental deaths	0	0	0	0	0
Killed in extremis	5	0	0	1	0
Natural deaths	68	44	33	40	47
Animals surviving to study termination[a]	77	31	42	34	28
Kaplan-Meier endpoint survival rate (%)	51	41	56	45	37
Survival analysis (p-value)	0.04[b]				
FEMALE					
Animals initially on study	150	75	75	75	75
Accidental deaths	0	0	0	0	0
Killed in extremis	4	5	1	2	3
Natural deaths	81	41	41	48	53
Animals surviving to study termination[a]	65	29	33	25	19
Kaplan-Meier endpoint survival rate (%)	43	39	44	33	25
Survival analysis (p-value)	0.004[b]				

a: Based on number of mice surviving to scheduled sacrifice
b: Result of the trend test using dose proportional scores.

There were no clinical signs in any f gr or in m dosed ≤100mg/kg. The only drug related finding was in HDm where a small incr in frequency of wet and/or stained abdominal area and piloerection were seen.
Palpable mass: the first palpable mass was found at wk 23 in 1m dosed 100mg/kg; no evidence of drug related effect on this parameter was noted.
B.wt/Food Intake: a sig and dose-dependent incr in mean B.wt was seen in m and f starting on wks 1-2 of dosing and lasting till wk54 in m and wk80 in f. These incr in m were mild ranged between 2-7% compared to the combined cont but greater incr noted in f specially those in higher doses: 2-6% at 25mg/kg and 12-15% at ≥ 50mg/kg. The increases in mean B.wt were drug related but not considered of biological sig in all m drug grs and f dosed 25mg/kg but biologically and toxicologically sig in f dosed 100&200mg/kg since these grs showed histopath findings (liver adenomas in f).

Accompanying the incr in mean B.wt, mean food intake was also incr in m at ≥100mg/kg/d and in f at ≥50mg/kg/d. These incr were drug related and occurred mainly during the 1st 15wks of dosing and ranged between 2-16% higher than the values for the combined cont.
Hematology: no drug related findings.
Organ wts: not done on any organ or tissue of any gr.
Gross Findings: the following were seen rel to the cont:
Lungs - discolored areas: in f dosed 100&200mg/kg at 25/75 and 28/75 respectively vs. incidence of 14&16 out of 75 each in cont. The incr in lung discoloration in HDf was contributed to incr incidence of intersitial pneumonia in these mice. The lung discoloration was considered not drug related since it was seen in all mice including the

Mouse dietary 2yr car (Cont.)

2 cont grs of both sexes and the incidence did not incr when all mice in the study were grouped together.
Liver - mass: 9/75 in f dosed 200mg/kg vs. 3/75 in f cont. This was correlated with histopath finding of increased adenomas.
Urinary Bladder - distended: m incidence 20, 16, 15, 25 of 75 each compared to 8&12 of 75 in the 2 cont grs. This finding was considered incidental since it was not dose related and not correlated to any histopath findings in this organ.
Histopathology: the following table from the sponsor presents (in %) the incidence of ***NON-NEOPLASTIC*** lesions in ***UNSCHEDULED DEATHS***:

INCIDENCE TABLE OF SELECTED NON-NEOPLASTIC LESIONS - UNSCHEDULED DEATHS (%)

	MALES						FEMALES					
Dose Group	1	2	3	4	5	6	1	2	3	4	5	6
N° Animals/group	75	75	75	75	75	75	75	75	75	75	75	75
N° Animals Examined	39	34	44	32	41	47	42	43	48	42	50	56
Dose (mg/kg/day)	0	0	25	50	100	200	0	0	25	50	100	200
MESENTERIC NODE												
- Depletion, lymphoid	2.6	10.3	9.4	7.1	15.7	4.3	2.6	2.5	12.5	15.6	16.3	5.8
SPLEEN												
- Depletion, lymphoid	18.4	28.1	42.9	41.0	29.4	17.4	9.8	0	17.0	10.0	18.4	17.9
ADRENAL MEDULLA												
- Hyperplasia	0	0	0	0	0	1.2	0	0	0	0	2.0	1.8
LUNGS												
- Hemorrhage	5.1	5.9	18.2	12.5	7.3	4.3	4.8	7.0	6.5	4.8	12.0	14.3
- Pneumonia, interstitial	5.1	8.8	22.7	12.5	19.5	10.6	4.8	11.6	12.6	11.9	28.0	23.2
LIVER												
- Eosinophilic Foci	2.7	0	0	0	2.4	0	0	0	2.2	2.5	2.0	1.8
- Necrosis, hepatocellular	8.1	6.1	6.8	9.4	2.4	10.6	2.4	4.7	4.3	5.0	8.0	7.1
- Hypertrophy, centrolobular	0	0	2.3	0	2.4	2.1	0	0	0	0	2.0	0
PROSTATE GLAND												
- Prostatitis, purulent	0	0	0	0	2.4	0.0	-	-	-	-	-	-
SEMINAL VESICLES												
- Dilated	28.9	18.2	31.0	33.3	31.0	42.6	-	-	-	-	-	-
- Atrophy, diffuse	0	0	2.4	3.2	7.0	4.3	-	-	-	-	-	-
OVARIES												
- Atrophy	-	-	-	-	-	-	7.1	4.7	6.7	7.5	24.0	12.5

The incidence of eosinophilic foci of the liver in f was: 1/46, 1/42, 1/50, and 2/56 in 25, 50, 100, & 200mg/kg dose grs with no finding in the cont. but these foci were present in m cont gr at 2.7%. The incidence of centrolobular hypertrophy in m was as follows: 1/44, 1/41, & 4/47 in 25, 100 & 200mg/kg grs and in 1f dosed 100mg/kg but not in m or f cont grs. The hepatocellular necrosis was considered not drug related because (1) the incidence was within the historical cont range in this lab for f that are found dead (12.5%), (2) no incr incidence was found at final kill or when all mice (unscheduled and final kill) were evaluated together and, the incr in f was not dose-dependent in f though it was in the 2 high dose grs in m (2.4 vs. 8.5% respectively).

Mouse dietary 2yr car (Cont.)

The other reported findings (lymphoid depletion in mesenteric node, spleen, hyperplasia of the adrenal medulla, lung hemorrhage, prostitis, dilated and atrophied seminal vesicles, and atrophied ovaries, and intersitial pneumonia) were considered incidental and they are commonly occurring spontaneous lesions in mice.

The incidences of ***NEOPLASTIC LESIONS*** in ***UNSCHEDULED deaths*** (%; # of mice with ≥1 lesions divided by # of mice where the tissue/organ was examined x 100), were as follows (table from sponsor):

INCIDENCE TABLE OF SELECTED NEOPLASTIC LESIONS - UNSCHEDULED DEATHS (%)

	MALES						FEMALES					
Dose Group	1	2	3	4	5	6	1	2	3	4	5	6
N° Animals/group	75	75	75	75	75	75	75	75	75	75	75	75
N° Animals Examined	39	34	44	33	41	47	42	43	46	42	50	56
Dose (mg/kg/day)	0	0	25	50	100	200	0	0	25	50	100	200
SKIN												
- Sarcoma*	0	0	0	0	0	2.1	0	0	0	0	2.0	1.8
HEMOLYMPHO-RETICULAR SYSTEM												
- Histocytic sarcoma	0	0	0	3.0	2.4	6.3	9.5	11.6	13.0	11.9	12.0	8.9
- Hemangioma	2.6	0	0	3.0	0	0	0	0	0	2.4	2.0	1.8
PANCREAS												
-Adenoma, Islet cell	0	0	0	0	0	0	0	0	0	0	0	1.9
-Carcinoma, Islet cell	0	0	0	0	0	2.1	0	0	0	0	0	0
LUNGS												
- Carcinoma, bronchoalveolar	2.6	5.9	2.3	0	17.1	10.6	4.8	7.0	2.2	0	8.0	7.1
- Adenoma, bronchoalveolar	25.6	17.6	18.2	15.6	14.6	10.1	11.9	9.3	19.6	11.9	22.0	12.5
JEJUNUM												
- Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	3.7
LIVER												
- Adenoma, hepatocellular	18.9	6.1	4.5	6.3	4.9	12.8	0	0	4.3	0	0	8.9
SEMINAL VESICLE												
- Leiomyoma	0	0	0	0	0	1.1	-	-	-	-	-	-

Uterus sarcoma: 1.8% in HDf. zero incidence in any other gr including the cont.
Bone osteosarcoma: 2.9% in m cont#2; 1.8% in HDf; zero incidence in all other grs.

* sarcoma or fibrosarcoma.

Liver: **hepatocellular adenomas in f** were drug related finding. The incidence was 5/56 in HDf and 2/46 in LDf. none in cont.
Lung: bronchoalveolar carcinoma was seen in 7/41 and 5/47 m dosed 100&200mg/kg compared to 1/39 & 2/34 mice in the cont. This finding was not dose dependent in either sex.
Findings in the lung. hemoreticular system, pancreas, seminal vesicles, uterus, and bone were considered not drug related and incidental because they were within historical range in this lab and not dose dependent.

Mouse dietary 2yr car (Cont.)

Histopath in ***SCHEDULED SACRIFICE*** (terminal) animals. Table below from the sponsor presents (in %) the incidence of ***NON-NEOPLASTIC*** lesions in ***FINAL SACRIFICEacrifice*** *mice:*

INCIDENCE TABLE OF SELECTED NON-NEOPLASTIC LESIONS - FINAL SACRIFICE (%)

	MALES						FEMALES					
Dose Group	1	2	3	4	5	6	1	2	3	4	5	6
N° Animals/group	75	75	75	75	75	75	75	75	75	75	75	75
N° Animals Examined	36	41	31	42	34	28	33	32	25	33	25	19
Dose (mg/kg/day)	0	0	25	50	100	200	0	0	25	50	100	200
SALIVARY GLANDS												
- Infiltrate, mononuclear	16.7	14.6	25.8	26.2	29.4	35.7	24.2	21.9	16.3	15.2	24.0	10.5
MESENTERIC NODE												
- Extramedullary hematopoiesis	0	2.5	3.2	2.4	5.0	7.1	0	0	0	0	0	10.5
- Cystic degeneration	0	0	0	0	0	0	0	0	0	3.0	0	5.3
LUNGS												
- Infiltrate, mononuclear	19.4	9.8	19.4	14.3	35.3	39.3	18.2	15.6	34.3	30.3	8.0	5.3
STOMACH												
-Dilated glands	2.8	2.4	0	4.8	5.9	7.1	3.0	3.1	4.0	0	0	0
LIVER												
- Focus, eosinophilic	5.6	4.9	0	2.4	0	0	0	0	0	0	4.0	10.5
- Hypertrophy, centrolob.	0	4.9	0	4.8	0	10.7	0	0	0	0	0	0
- Necrosis, individual cell	2.8	0	0	0	0	0	0	0	4.0	0	0	5.3
- Proliferation, oval cell	2.8	0	0	4.8	0	7.1	0	0	0	0	0	0
URINARY BLADDER												
- Dilation	8.3	7.5	6.5	9.5	0	7.1	0	0	0	0	0	5.3

The incidence of eosinophilic foci in the liver increased dose dependently in f dosed 100mg/kg (1/25) and 200mg/kg (2/19); zero in cont, and the incidence of centrolobular hypertrophy was incr only in HDm (3/28) compared with the incidence in 1 cont gr (2/41; the other cont had zero incidence). Both findings were considered drug related. The incr in eosinophilic foci in f correlated with the hepatocellular adenomas in f. The centrolobular hypertrophy is a known drug effect in rodents.

The other findings reported in the table were not drug related because they are incidental, commonly occurring spontaneous lesions in the mouse and the incidences fell within that of the historical range. The dose dependent incr in extramedullary hematopoeisis of the mesenteric node in m and in HDf was not observed in other organs and therefore, considered by the sponsor to be not-drug related: the reviewer however, does not exclude a drug effect.

Mouse dietary 2yr car (Cont.)

The incidences of ***NEOPLASTIC LESIONS*** in ***SCHEDULED DEATHS*** are as follows (table from sponsor):

INCIDENCE OF SELECTED NEOPLASTIC LESIONS - FINAL SACRIFICE ANIMALS (%)

	MALES						FEMALES					
Dose Group	1	2	3	4	5	6	1	2	3	4	5	6
N° Animals/group	75	75	75	75	75	75	75	75	75	75	75	75
N° Animals Examined	36	41	31	42	34	28	33	32	29	43	25	19
Dose (mg/kg/day)	0	0	25	50	100	200	0	0	25	50	100	200
SKIN												
- Fibrosarcoma	0	2.4	0	0	0	0	0	0	0	0	0	5.3
HEMO-LYMPHORETICULAR												
- Histiocytic Sarcoma	0	0	0	2.4	0	0	0	3.1	3.4	6.1	16.0	0
LIVER												
- Adenoma, hepatocellular	22.2	19.5	12.9	19.0	29.5	25.0	6.1	0	3.4	2.0	16.0	21.1
SEMINAL VESICLES												
- Adenoma	0	0	0	0	0	3.6	-	-	-	-	-	-
UTERUS												
- Leiomyoma	-	-	-	-	-	-	0	0	3.4	2.0	4.0	5.3
OVARIES												
- Adenoma, tubular	-	-	-	-	-	-	0	0	0	0	0	5.3
- Cystadenoma	-	-	-	-	-	-	0	0	6.9	2.0	8.0	5.3
VAGINA												
- Adenoma, leiomyosarcoma	-	-	-	-	-	-	0	0	0	0	0	5.3
BRAIN												
- Meningioma	0	0	0	0	0	0	0	0	0	0	0	5.3

The only drug related neoplasia was **liver adenomas in MD&HDf**. This incidence was 4/25 in 100mg/kg and 4/19 in 200mg/kg females compared to 2/33 in 1 cont gr and 0/32 in the 2nd cont gr. The sponsor indicated that all other tumors were not drug related because their incidence either fell within historical range or the incr was not dose dependent.

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Mouse dietary 2yr car (Cont.)

The following table from the sponsor presents ***NON-NEOPLASTIC*** lesions from ***ALL ANIMALS*** in the study:

INCIDENCE OF NON-NEOPLASTIC LESIONS - ALL ANIMALS (%)

	MALES						FEMALES					
Dose Group	1	2	3	4	5	6	1	2	3	4	5	6
N° Animals/group	75	75	75	75	75	75	75	75	75	75	75	75
Dose (mg/kg/day)	0	0	25	50	100	200	0	0	25	50	100	200
LUNGS												
-Pneumonia, interstitial	5.3	9.3	18.7	8.1	16.0	8.0	4.0	10.7	21.3	8.0	20.0	21.3
LIVER												
- Eosinophilic foci	4.1	2.7	0	1.4	1.3	0	0	0	1.3	1.4	2.7	5.3
- Hypertrophy, centrolobular	0	2.7	1.3	2.7	1.3	9.3	0	0	0	0	1.3	0
- Regenerative hyperplasia	1.4	4.1	2.7	2.7	0	0	1.4	0	1.3	0	0	2.7
- Congestion	0	0	1.3	0	0	0	0	0	0	0	1.3	5.3
URINARY BLADDER												
- Dilation	10.8	18.1	24.6	26.1	20.9	29.3	4.4	2.9	9.7	1.5	7.5	10.6
EYES												
- Mineralization	1.7	1.5	6.8	3.2	1.8	7.0	1.8	1.8	5.1	0.9	10.4	7.8
- Infiltrate, mononuclear	0	0	0	0	0	5.3	1.9	1.8	1.7	0	2.1	0

The liver eosinophilic foci incidence in all f incr dose dependently and an incr in incidence of centrolobular hypertrophy was seen in HDm, both findings considered to be drug related. The eosinophilic foci incidence in f was 1/75, 1/73, 2/75, and 4/75 in 25, 50, 100, and 200mg/kg respectively. The incidence of centrolobular hypertrophy in m dosed 200mg/kg was 7/75 compared with 2/74 and 0/75 in the 2 controls. Regenerative hyperplasia was not affected in livers from m mice, however, a slight incr noted in HDf 2/75 vs. 1/74 in cont; incidence of liver congestion was incr in HDf.

The urinary bladder dilation incidence was incr in all m drug grs and in f dosed 25, 100, and 200mg/kg. The sponsor indicated there was no obstructive lesions in the lower urinary tracts in either sex and no evidence of smooth muscle atony. Therefore, the sponsor considered this finding to be of "no biological sig but of biological variability". However, it is the opinion of the reviewer that this finding maybe of toxicologiccal sig.

All other lesions were considered spontaneously occurring lesions and not drug related because they fell within historical cont ranges or not dose dependent or noted in a single sex.

Mouse dietary 2yr car (Cont.)

The following table from the sponsor presents ***NEOPLASTIC*** lesions from ***ALL ANIMALS*** in the study:

INCIDENCE OF SELECTED NEOPLASTIC LESIONS - ALL ANIMALS (%)

	MALES						FEMALES					
Dose Group	1	2	3	4	5	6	1	2	3	4	5	6
N° Animals/group	75	75	75	75	75	75	75	75	75	75	75	75
Dose (mg/kg/day)	0	0	25	50	100	200	0	0	25	50	100	200
SKIN												
- Sarcoma/fibrosarcoma	0	1.4	0	0	0	1.3	0	0	1.4	0	1.3	2.7
HEMOLYMPHO-RETICULAR SYSTEM												
- Malignant Lymphoma	6.7	4.0	4.0	1.3	8.0	10.7	10.7	22.7	21.3	25.3	16.0	14.7
- Histiocytic Sarcoma	0	0	0	2.7	1.3	2.7	5.3	8.0	9.3	9.3	13.3	6.7
PANCREAS												
- Carcinoma, islet cell	0	0	0	0	0	1.3	0	0	0	0	0	0
- Adenoma, islet cell	0	0	0	0	0	0	0	0	0	0	0	1.4
LUNGS												
- Carcinoma, bronchoalveolar	4.0	4.0	5.3	4.1	9.3	8.0	4.0	6.7	1.3	0	5.3	5.3
- Adenoma, bronchoalveolar	26.7	32.0	28.0	21.6	26.7	11.3	10.7	20.0	18.7	16.0	24.0	16.0
JEJUNUM												
- Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	1.3
LIVER												
- Carcinoma, hepatocellular	4.1	9.9	4.7	6.8	6.7	6.7	0	0	0	1.4	1.3	0
- Adenoma, hepatocellular	20.5	13.5	8.0	13.5	13.3	17.3	2.7	0	4.0	1.4	5.3	12.0
SEMINAL VESICLES												
- Adenoma	0	0	0	0	0	1.3	-	-	-	-	-	-
OVARIES												
- Cystadenoma	-	-	-	-	-	-	0	0	2.9	1.4	2.7	1.3
- Tubular adenoma	-	-	-	-	-	-	0	0	0	0	0	1.3

Vagina - adenoma, basosequamous 1.3% HDf, zero incidence in all other grs including cont.
Brain - meningioma 1.3% HDf. zero incidence in all other grs including cont.
Bone - osteosarcoma 1.3% HDf, zero incidence in all other grs including cont.
1.3% in 1 of the 2 cont grs, zero in all other grs.

The following tumors were seen in drug grs but not in the cont and in some cases statistical sig was achieved however, the values were within the historical range for that tumor:

- skin sarcoma or fibrosarcoma in f dosed 200mg/kg (p=0.02)
- hemolymphoreticular system: malignant lymphomas in m dosed 200mg/kg (p=0.02).
  Histocytic sarcoma in m dosed 100&200mg/kg (p=0.04&0.06).
- lungs: bronchoalveolar carcinoma in m dosed 200mg/kg (p=0.04).
  Combined bronchoalveolar adenoma and carcinoma in m (p=0.33).
- liver: hepatocellular adenomas in f dosed 200mg/kg (p<0.001).

Mouse dietary 2yr car (Cont.)

From the table below, it can be seen that except for the liver adenomas in f, all other tumor incidence fell within the historical range from [redacted] but not those from [redacted].

STATISTICALLY SIGNIFICANT NEOPLASMS-STUDY N 450 (Incidences are expressed in percentages)

CL 284,846 Mouse (SN 450)					Historical Control*	
Tumor	Sex	Dose mg/kg/day	p** (Test)**	Incidence	[redacted] range)	[redacted]
Hepatocellular Adenomas	F	0.0		2.7,0		
	F	25		4.0		
	F	50		1.4		
	F	100		5.3		
	F	200	<0.001 (Pairwise)	12.0	3.13 (0-11.27)	1.5
Malignant Lymphoma	M	0.0		6.7,4.0		
	M	25		4.0		
	M	50		1.3		
	M	100		8.0		
	M	200	0.02 (Pairwise)	10.7	9.91 (0-12.0)	5.75
Histocytic Sarcoma	M	0.0		3.0		
	M	25		0		
	M	50		2.7		
	M	100	0.04 (Exact ordinal scale)	1.3		
	M	200	0.06 (Exact dose scale)	2.7	1.69 (0-7.69)	0.5
Bronchoalv. Carcinoma	M	0.0		4.0,4.0		
	M	25		5.3		
	M	50		4.1		
	M	100		9.3		
	M	200	0.04 (Pairwise)	8.0	11.07 (1-20.0)	13.0
Combined Bronchoalv. Adenoma & Carcinoma	M		0.33 (Pairwise)			
Sarcoma or Fibrosarcoma, skin	F	0.0		0.0		
	F	25		1.4		
	F	50		0		
	F	100		1.3		
	F	200	0.02 (exact)	2.7	0-3.9****	0-2.0****

* Spontaneous Neoplastic Lesions in the Crl:CD-1(ICR) [redacted] March 1995 and Background Tumor Incidences from Carcinogenicity Studies Crl:CD-1 Swiss [redacted] February 1995.

** p-values quoted in dose proportional scaling.

*** [redacted] ranges are quoted for "sarcoma", skin.

**** [redacted] data includes all mesodermal skin tumors.

The incr in hepatocellular adenomas in f dosed 100mg/kg (4/75) and 200mg/kg (9/75) rel to the cont (0/75 & 2/74 for the 2 grs), was considered drug related and the values were above the historical range. The incr in liver carcinomas in males of all doses and f dosed 50&100mg/kg. was not dose dependent.