- Secondary actions of tolterodine in the conscious dog and mouse have only been recorded after oral administration of high doses, resulting in high serum levels of both tolterodine and DD 01.

- In the conscious dog, an increased heart rate was recorded at unbound serum concentrations of tolterodine and DD 01 that were 17 and 7 times, respectively, higher than those expected to be reached in most patients treated with tolterodine 2 mg bid. The corresponding ratios for effects on the EGG (QT-prolongation) were 100 for tolterodine and 40 for DD 01. Almost the same ratios (>100 and >30) were found for the unbound concentrations at which effects on the central nervous system, gastrointestinal tract and renal function were recorded in the mouse.

- Poor metabolizers of tolterodine will get higher concentrations of tolterodine, but no measurable levels of DD 01. Similarly, the serum levels of tolterodine and DD 01 may be affected by drug interactions. This issue cannot be adequately addressed in animal studies and has therefore been studied in humans.

- Most of the secondary effects are of an antimuscarinic nature. Thus, increased heart rate, increased locomotor activity, mydriasis, decreased intestinal motility and development of residual urine can all be attributed to blockade of muscarinic receptors.

PHARMACOKINETICS/TOXICOKINETICS

Summary of PK/TK:
Pharmacokinetics of tolterodine has been studied in rat, mouse and dog.

Differences between species were seen in systemic exposure. At similar oral doses, the serum concentrations of tolterodine in the dog were more than 50 and 30 times higher compared to rat and mouse respectively. The serum concentration in man was, after adjustment to the much higher dose given in the animals, in the same range as seen in the dog. With increasing dose, there was an non-proportional increase in Cmax and AUC in mouse and dog. The differences seen between species in the exposure of tolterodine was reduced when a comparison was based on unbound concentration in serum.

The binding to serum proteins varied between the species. The unbound fraction was in dog and cat less than 1% but in rodents between 7.9-20.1%. In man the unbound fraction was 2.1%. Orosomucoid was found to be a major binding protein.

Tolterodine was extensively metabolized. The metabolic pathway in dog and mouse was similar to that in man. The main metabolic pathway was
In rat another metabolic pathway involving hydroxylation of the unsubstituted aromatic ring was found.

The 5-hydroxymethyl metabolite (DD 01) has been shown to be pharmacologically active. In dog and mouse the serum concentration of the metabolite ranged from the same to four times lower the concentration of the parent molecule; in man the metabolite ranged from about equal concentrations to not measurable concentrations. The protein binding of the metabolite was however much lower than that of tolterodine, resulting in a higher unbound concentration in serum of the metabolite compared with tolterodine (4-10 fold) in dog and mouse.

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The excretion of radioactive material in urine was, after an oral dose of radioactively labeled tolterodine (4 mg/kg bw) 9% in the rat, 50% in the dog, and in man 75% of a dose of 5 mg. Most of the radioactivity represented metabolites, mainly the carboxylated metabolite, while the parent molecule was present only in low amounts. After an iv dose in the rat, the main part of the radioactivity was found in feces (75%) indicating a high biliary excretion in this species.

In conclusion, mouse and in particular dog, exhibit similarities to man regarding pharmacokinetic profile and metabolite pattern.

Systemic exposure: At the no-observed-adverse effect doses in general toxicology studies

	Mouse	Dog	Man
Dose	10 mg/kg	0.5 mg/kg	2 mg bid
tolterodine	fu=16%	fu=2.1%	fu=3.7%
Cmax	83	65	3.6
Cmax u	13	1.4	0.13
AUC	238	166	17
AUC u	38	3.5	0.63
DD01	fu=72%	fu=32%	fu=36%
Cmax	63	12	2.9
Cmax u	45	3.8	1.0
AUC	166	52	14
AUC u	119	17	5.0

Concentrations in ug/l, fu = unbound fraction in serum, u = unbound concentration, n.d. = undetectable. AUC is estimated for a dose interval of 24 hrs in animals and 12 hrs in man. To compare exposures between humans and animals, the human AUC should be doubled.

Systemic exposure: At the highest doses in the carcinogenicity studies.

	Mouse	Rat		Man
Dose	30 mg/kg	20 mg/kg (F)	30 mg/kg (M)	2 mg bid
tolterodine	fu=16%	fu=22%		fu=3.7%
Cmax	18	14	23	3.6
Cmax u	2.9	3.1	5.1	0.13
AUC	355	291	462	17
AUC u	57	64	102	0.63
DD01	fu=72%	fu=63%		fu=36%
Cmax	10	n.d.	n.d.	2.9
Cmax u	7.2			1.0
AUC	198			14
AUC u	143			5.0

concentrations in ug/l; u=unbound concentration; fu=fraction unbound; n.d.=not detectable; AUC in animals over 24 hrs, man over 12 hrs.

Pharmacokinetic parameters of tolterodine

Species	fu %	t1/2 h	Vd l/kg	Vdu	CL	Clu	Urinary	Fecal	Bioavail

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					l/hxkg		Excretion 14C	Excretion 14C	ability %
Mouse	16	1.0	16	100	13	81	43	51	10-20
Dog	2.1	0.8	1.5	71	1.4	67	50	34	60
Rat	22	1.8	25		10		17	81	2-20
Man	3.7	3.7	1.6	43	0.64	17	77	17	17

fu=fraction unbound
Vdu= volume of distribution (unbound concentration)
CL=clearance; Clu= clearance (unbound concentration)

Metabolism

Metabolite screening for urinary metabolites of tolterodine has been performed in mouse, rat, dog and man. The urine was analyzed by The isolated metabolites in the

Tolterodine was extensively metabolized. The metabolite pattern in dog and mouse urine was similar to that of human urine while rat urine exhibited a markedly different pattern. Tolterodine is primarily metabolized by The major metabolites that were identified in both mouse, dog and man were the

The rat appears to metabolize tolterodine along a different route

metabolites were observed.

Excretion of radioactivity in urine and feces after administration of 14C-labelled tolterodine was studied in rat and in dog. The total recovery in the studies was >95% in the rat and > 80% in the dog.

In the rat, both intravenous (0.4 mg/kg bw) and oral doses (4, 12 and 40 mg/kg bw) were given. After the iv dose, an average of 75% of the dose was found in feces indicating a high biliary excretion. After the oral doses the main part, 90%, was excreted after the first 24 hours, mainly in the feces. An average of 9-24% was found in the urine; increasing amount with increasing dose in the interval 4-40 mg/kg bw. In the dog, only oral doses (0.5 and 4.5 mg/kg) were studied. A larger amount, about 50% of the dose, was excreted in the urine. In man, 75% of a tracer dose of 14C-labelled tolterodine (total dose 5 mg) was excreted in urine and 20% in feces.

Most of the radioactivity in urine represented metabolites, mainly the metabolite in man and dog. The parent molecule was present only in low amounts.

The pharmacokinetics of tolterodine was studied in rat, mouse and dog. There were large differences in systemic exposure between the species investigated. These differences were eliminated when based on unbound fraction of tolterodine in serum, as there were large differences in protein binding between the species. The rat differed from the other species by a different metabolic pathway.

Mouse and in particular dog exhibited similarities to man regarding pharmacokinetic profile and metabolite pattern.

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TOXICOLOGY

Single and repeat dose toxicology: Acute Toxicity in mice and rats after single oral administration of Tolterodine.

Study sponsor:
Study report number: 89-22
Date: 1990
Species/strain: mice and Sprague-Dawley rats
Route: Oral gavage
Number/sex/dose: 5
Doses: 150 and 300 mg/kg for mice and 150, 300 or 375 mg/kg for rats
Duration: single dose with 14 day observation period.

There were no deaths in LD mice and 60% mortality at the high dose. All deaths occurred within 24 hrs of dosing. There was no morality in the rat study. There was a reduction in food consumption and body weight loss in the first few days after treatment in both mice and rats at all dose levels.

Acute intravenous toxicity study in the mouse.

Testing facility: Pharmacia Therapeutics Uppsala
Study number: number 93059
Date: 1994
Species/strain: mice
Route: intravenous
Number/sex/dose: 5
Doses: 8, 16 and 24 mg/kg
Duration: single administration with 14 day observation period.

No reaction to treatment at 8 mg/kg. In males treated with 16 mg/kg increased motor activity, increased respiratory frequency, piloerection and ventral recumbency was observed for short periods after dosing. One male died after having convulsions. No effects in females at this dose. Both males and females treated with 24 mg/kg showed ataxia, ventral recumbency and convulsions. An 80% mortality was recorded at this dose level.

Acute intravenous toxicity study in the rat

Testing facility: Pharmacia Therapeutics Uppsala
Study number: number 93058
Date: 1994
Species/strain: Sprague-Dawley rats
Route: intravenous
Number/sex/dose: 5
Doses: 8, 16 and 24 mg/kg
Duration: single administration with 14 day observation period.

No effects of treatment with 8 mg/kg. At 16 mg/kg, only short-lived ataxia. At 24 mg/kg there were deaths (2/5 males and 1/5 females) which occurred during or immediately after dosing. The most prominent clinical findings at 24 mg/kg were reversible ataxia, ventral recumbency and convulsions.

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Repeated Dose Toxicology

Toxicity to mice by repeated oral administration for 13 weeks followed by a 4-week recovery period.

Study sponsor:
Study report number: document 20817F
Date: 1993
Species/strain: CD-1(ICR)BR mice
Route: Oral gavage
Number/sex: 16, with an additional 6/sex for recovery and 24-30/sex for toxicokinetics and metabolism studies.
Doses: 4, 12 or 40 mg/kg
Duration: 13 weeks with 4 week recovery

Mortality: Significant increase in the HD gps. No consistent findings to account for the deaths. Sponsor concludes that deaths due to pharmacological (anticholinergic) effect of the drug.

Clinical signs: None

Bodyweight changes: A significant reduction in bw gain at the HD for males and females. Sponsor did not consider the reduction to be toxicologically significant and simply reflected normal variability for mice of their age and strain at these labs.

Food consumption: No treatment related effect.

Water consumption: During wks 8 and 12, the HD animals consumed more water than controls.

Hematology: No treatment related effects.

Clin chem: No toxicologically significant changes.

Urinalysis: No toxicologically significant changes.

Gross path: No treatment related effects.

Organ wts: No toxicologically significant findings.

Histopathology: Abnormal round spermatids in 6/13 HD males compared to 3/16 control males. LD and MD were similar to controls. Testicular atrophy, prominent interstitial cells and minimal reduction of spermatogenesis was seen in low incidence in treated males but not in controls. Sponsor states that these changes are occasionally seen in controls and believe the changes are unrelated to treatment.

General toxicity in rats of tolterodine administered orally for two weeks.

Study sponsor:
Study number: document 89 96 616
Date: 1990
Species/strain: Sprague-Dawley rats
Route: Oral gavage
Number/sex/dose: 10
Doses: 4, 12 or 40 mg/kg
Duration: 2 weeks

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Mortality: None treatment related.

Clinical signs: Salivation, occasionally red-stained, showed a dose related incidence and appeared usually within 5-15 minutes of dosing. It continued throughout the study.

Body weight: No effect.

Food consumption: No effect.

Hematology: Slight stimulation of erythropoiesis in males only. Increased platelet counts in HD males and females. Increase in WBC counts in HD males and females as well as LD females.

Clinical chemistry: No toxicologically significant changes.

Urinalysis: Reduced volume of urine and increased osmolality, density and protein concentration were seen in MD and HD males. HD females had a slightly increased volume of urine when compared to controls.

Organ wts: Small but significant increase in absolute and rel liver wts for HD males and females and MD females.

Gross pathology: No effects.

Histopathology: No toxicologically significant changes.

Toxicity to rats by repeated oral administration for 13 weeks followed by a 4-week recovery period.

Study sponsor:
Study number: 90
Date: 1991
Species/strain: CD(SD) BR rats
Route: Oral gavage
Number/sex/dose: 15
Doses: 4, 12 or 40
Duration: 13 weeks with a 4 week recovery period.

Mortality: Ten HD females died during the study. All died approximately 20 hrs after dosing. Prior to death none had displayed any obvious clinical signs of debility or intoxication. Neither macroscopic post mortem exam nor histopath exam revealed any changes that could account for the deaths.

Clinical signs: Dose related salivation together with brown staining on the muzzle and wetting of the coat.

Body weight: HD females gained less than controls. No other effects.

Food consumption: No significant effects.

Ophthalmoscopy: No effects.

Hematology: MD and HD females had a significantly lower WBC count than controls.

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Clinical chem: Dose related increase in plasma cholesterol in HD rats. Some increase in plasma triglycerides also noted. Alk Phos increased in MD and HD females.

Urinalysis: HD males had more dilute urine with lower sp gravity and osmolality. Females also affected but to a lesser degree.

Gross path: No treatment related changes.

Organ weights: Increased liver wts for MD and HD females and HD males. Increased lung wts for HD rats and increased kidney wts for HD males.

Histopathology: Thyroid - Increased height of follicular epithelium and decrease colloid in HD rats.
Liver - centrilobular and/or diffuse hepatocyte enlargement in MD and HD males and females.
Lungs - Prominent, pigmented (iron positive) alveolar macrophages in MD and HD males and HD females.
Only the lung pathology was apparent after the 4 week recovery period.

General toxicity in dogs of tolterodine administered orally for two weeks.

Study sponsor:
Study number: 89 96 631
Date: 1990
Species/strain: Beagle dogs
Route: Oral capsules
Number/sex/dose: 2
Doses: 0.5, 2 or 8 mg/kg
Duration: 2 weeks

Mortality: None.

Clinical signs: Main clinical signs were those related to the anticholinergic effects of the drug; inhibition of salivation, pupil dilation and discharge from the eyes. Ataxia and drowsiness were also observed on the first day of treatment in one HD dog. Also, a low frequency of vomiting was noted among the treated dogs.

Body wts: Reduction in body wt was seen for one male and one female of the HD.

Food consumption: Reduced in HD dogs.

Ophthalmoscopic exam: No effects.

Electrocardiography: No significant effects.

Hematology: No significant effects.

Clin chem: No significant effects.

Urinalysis: Increased vol with decreased osmolality in HD dogs.

Organ wts: No effects.

Histopathology: Conjunctivitis in all HD dogs. No other treatment related effects.

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Toxicity to dogs by repeated oral administration for 13 weeks.

Study sponsor:
Study number: document 91 96 112
Date: 1991
Species/strain: Beagle dogs
Route: Oral capsules
Number/sex/dose: 4
Doses: 0.5, 1.5 or 4.5
Duration 13 weeks

Mortality: None

Clinical signs: Dry mouth, pupil dilation and discharge from the eyes. All HD dogs developed conjunctivitis. Some ptosis and ataxia in 2 HD dogs on day 1 of treatment only.

Body weight: No changes.

Food/water consumption: No effects.

Ophthalmoscopy: No effects other than conjunctivitis.

EKG: No effects.

Hematology: No effects.

Clin chem: No effects.

Urinalysis: No effects.

Gross path: No effects.

Organ weights: No effects.

Histopathology: No treatment related findings.

Toxicity to Beagle dogs by repeated oral administration for 26 weeks.

Study sponsor:
Study number: 91084
Date: 1991-2
Species/strain: Beagle dogs
Route: Oral capsules
Number/sex/dose: 5
Doses: 0.5, 1.5 or 4.5 mg/kg
Duration: 26 weeks

Mortality: One LD and one MD female were sacrificed moribund with pyometra and chronic disc prolapse, respectively. Neither were treatment related.

Clinical signs: Increased pupillary response (dilation) to direct light with the MD and HD. In the high dose the effect was moderate to pronounced and persisted for 24 hrs.

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Slight depression of salivation in the MD and slight to moderate in the HD. This occurred within the first 3-6 hrs after dosing particularly during the first week of treatment and sporadically after that.

There was dose-related decrease in tear flow; dry nose; increase in dry oral mucosa and corneal spots/ulcers. Corneal changes regressed with appropriate treatment. The HD dogs on the first day of dosing showed ataxia, sedation, sensitivity towards light and trembling which subsided by the following day. Thereafter only occasional ataxia and tremor were seen. In the HD, there were occasional distended abdomen and blood in the urine.

Bodyweight: No effect

Food consumption: No effect.

Hematology: No treatment related effects.

Clinical chemistry: There were sporadic changes in LFT's which were not dose and probably not treatment related.

Urinalysis: Some increase in urine volume in the MD and HD females.

Ophthalmologic exam: There was unilateral focal, superficial keratitis at 12 weeks in one control and 3 MD dogs. This was not seen in any dogs at 26 wks.

ECG: During the first hour after dosing, there was an increase in heart rate in most dogs. The lowest dose producing this effect was 1.5 mg/kg in males and 0.5 mg/kg in males. During the course of the study the dogs adapted and no treatment related effect on heart rate was noted.

The duration of the T wave was increased in HD males 1 hr after dosing. This effect was also seen in females and occurred about 1-5 hrs after dosing.

Organ weights: Statistically significant increased liver wt in HD males and non significant increase in HD females.

Gross path: Distended gall bladder with a large amount of bile was seen in one male and one female in the HD. Another HD female had a distended gall bladder with slightly increased amount of bile.

Histopathology: There were no histopath correlates to the enlarged livers. Aside from the two animals killed during the study, there were no toxicologically significant histopath changes.

52-week oral toxicity study in the beagle dog followed by an eight-week recovery period

Testing facility: Pharmacia & Upjohn, Helsingborg, Sweden
Study number: Study no. 95009
Date: 1996
Species/strain: Beagle
Route: Oral gelatin capsules
Number/sex/dose: 7 dogs/sex in the control and high dose and 5 dogs/sex in the low and mid doses. The extra two animals in the control and HD were assigned for an 8- week recovery period.
Doses: 0.5, 1.5 and 4.5 mg/kg/day
Duration: 52 weeks

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Systemic Exposure

Dose mg/kg	Week No.	Cmax (ng/ml)				AUC (ngxh/ml)			
		Male		Female		Male		Female	
		T	DD01	T	DD01	T	DD01	T	DD01
0.5	2	72.8	12.0	50.7	9.2	161	43.1	103	27.5
	26	87.9	15.3	61.9	12.8	178	52.1	160	47.0
	52	135	15.6	46.8	12.2	393	66.6	116	35.5
1.5	2	125	41.9	105	28.2	405	169	294	107
	26	190	49.3	136	35.1	538	212	363	125
	52	249	54.3	164	38.2	565	221	380	149
4.5	2	516	137	420	100	5989	1857	2894	1149
	26	695	148	574	127	4648	1975	3217	1349
	52	771	166	401	126	4276	2117	3981	1845

Mortality: Two high dose males showed subdued behavior, urinating difficulties, dilated tensed urinary bladder, blood-stained urine, distended abdomen and pain reaction at palpation of the abdomen caused by urolithiasis and were killed. One HD female showed a chronic purulent conjunctivitis, keratitis and half-closed eyes. The signs disappeared during a 27-days (days 183-210) dose free period but returned within a few days after start of dosing despite continuous moistening of the eyes. The dog was killed for ethical reasons on day 225.

Clinical signs: Dose related decreased pupillary response to directed light was seen from the LD upward. At the MD, pronounced dilation was observed in several dogs on several occasions. At the HD, slight to total dilation was seen in most dogs on most occasions. This effect normalized during the recovery period.

There was a dose-related decrease in salivary secretion and lacrimation starting at the LD.

At the HD, conjunctivitis and occasional corneal lesions due to dry eyes were seen in several dogs, pronounced in some dogs. After 2 months, daily moistening of the eyes of HD dogs was initiated.

Body Weight: No effects were seen.

Food Consumption: Slight decrease in HD females throughout the study and during recovery.

Ophthalmoscopy: Higher frequency of keratitis and/or corneal opacities and conjunctivitis in HD animals compared to controls or the other gps. Pupillary reflex was absent in several HD dogs after 6 or 12 months of dosing.

ECG-Recordings: On day 1 and 7, treated animals of both sexes showed increased heart rate one hr after drug administration. The lowest dose giving a significant increase was 0.5 mkd. During the course of the study the dogs adapted but treatment related effects on heart rate continued sporadically until the end of the study.

A decrease in the PQ-interval was seen in both sexes primarily after treatment with the MD and HD. The QRS-interval was unchanged. In both sexes given the MD and HD, the QT-interval

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decreased after the first dose (which may have been caused by the marked increase in heart rate). Both males and females showed changes in QTc during the treatment.

Hematology: No significant treatment related changes.

Clinical Chemistry: No treatment related changes.
Urinalysis: No treatment related changes.

Macroscopic Pathology: Two HD males had marked occlusive urolithiasis in the bladder and urethra along with mucosal hemorrhage and edema. Distention of the gall bladder with macroscopically normal bile was seen in some of the MD and HD male and female animals. Mucosal petechiation in the urinary bladder was seen in 1/3 and 2/5 HD males.

Organ Weights: No treatment related changes in absolute or relative organ weights were observed.

Histopathology: Two HD male dogs that were sacrificed had marked urolithiasis in the bladder and urethra which was the reason for the early sacrifice of these dogs. Mucosal and mural hemorrhage, necrosis and inflammation were seen in the urinary bladder and urethra. Both dogs had marked purulent hemorrhagic prostatitis along with inflammatory edema and congestion in the retroperitoneal soft tissues.

One HD female had corneal inflammatory cell infiltrate in both eyes and slight multifocal corneal epithelial degeneration in one eye. These changes were considered by the sponsor to be treatment related.

There was an inflammatory reaction in the urethra of both males and females which was possibly dose related. Foci of epididymal vascular and perivascular inflammation were seen in 1/5 males at the LD, 2/5 at the MD and 2/3 at the HD. Moderate chronic epididymitis was seen in another MD male.
No changes in the testis, epididymis, urinary bladder or urethra were seen in the recovery animals.

Discussion: The main adverse effects were due to tolterodine's pharmacological (antimuscarinic) effects, i.e. dry mouth, decreased tear flow and pupillary dilation. The ophthalmologic findings (keratitis, corneal opacities and conjunctivitis), seen mainly in the HD were most likely secondary to xerophthalmia induced by the antimuscarinic effects. The urolithiasis seen in two HD males was most likely secondary to increased residual urine, which predisposes to urinary infection, concrement formation and traumatic cystitis/urethritis.

Increase in heart rate was seen early in the study with some adaptation during the progress of the study but there was significant heart rate elevations in some dogs at various time points until the end of the study. Moreover, there was a general increase in heart rate (not reaching statistical significance) in almost all treated dogs at all time points throughout the study. There was no, no effect dose. Decreases in the PQ interval were probably the result of the increased heart rate.

Sub-Acute Toxicity to Mice by Dietary Administration for 13 Weeks.

Testing facility:
Study number: 9610715
Date: 10/96
Species/strain: CD-1 (ICR) BR mice
Route: oral; mixed with diet

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Number/sex/dose: 22/sex in control; 42/sex in treated. Only 10 animals/gp were used for toxicological evaluation. The remaining animals were used for toxicokinetics.
Doses: 4, 16, and 60 mg/kg/day
Duration: 13 weeks

Mortality: None treatment related.

Clinical signs: None related to treatment

Bodyweight: There was a non-significant decrease in BW gain in males and females.

	Group and Dosage (mg/kg/day)							
	male				female			
	0	4	16	60	0	4	16	60
week 0-13	11.0	15.3	10.8	8.0	7.9	7.5	6.7	6.0
SD	2.74	5.05	2.04	1.99	2.93	2.36	2.23	2.38

Food Consumption; No significance compared to controls.

Clinical chem/hematology: Some early morning elevations of T3 for HD males and females and elevations of T4 for HD males.

Organ weights: Slight increase in relative liver and pituitary weight for HD males. Mean thymus wts were decrease in HD females.

Gross pathology: No treatment related effects.

Histopathology: No changes correlated with the organ wt changes except for a minimal centrilobular hepatocyte enlargement in 1/10 LD, 1/10 MD and 3/10 HD male mice.

Sub-Acute Toxicity to Rats by Dietary Administration for 13 Weeks.

Testing facility:
Study number: 9610716
Date: 10/96
Species/strain: CD Sprague-Dawley BR Rats
Route: oral; mixed with diet
Number/sex/dose: 18/sex in control; 26/sex in treated. Only 10 animals/gp were used for toxicological evaluation. The remaining animals were used for toxicokinetics.
Doses: 4, 12, 40 mg/kg/day (M) and 4, 12, 24 mg/kg/day (F)
Duration: 13 weeks

Mortality: None

Clinical signs: No treatment related signs.

Bodyweight: Significant decrease in BW gain for HD males and females. At 13 weeks for males controls had gained 393 g vs 287 g for HD ($p < 0.01$). Control females gained 137 g vs 98 g for HD ($p < 0.01$).

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Food consumption: There was a significant ($p < 0.05$) decrease in FC for HD males only.

Clinical Chem/Hematology: No treatment related effects.

Organ weights: Increase in rel but not absolute liver wts for HD males and females. Mean lung wts were significantly increased for HD males and females.

Gross path: Congestion of the lungs was seen in 6/10 males and 4/10 females in the HD groups. Lung congestion was not seen in the controls. There was a decrease in adipose tissue for males and females that was dose related.

Histopathology: Lungs: Increased number of alveolar macrophages, some staining for iron, in 1/10 MD and 3/10 HD females. Increased incidence of vascular congestion in HD males and females.

Liver: Increased incidence of centrilobular hepatocyte enlargement in HD males and females.

Thyroid: Slightly higher incidence of increased height of follicular epithelium associated with decreased colloid in MD and HD males.

Sub-Acute Toxicity to Hamsters by Dietary Administration for 13 Weeks.

Testing facility:
Study number: 9610717
Date: 10/96
Species/strain: Hamsters
Route: oral; mixed with diet
Number/sex/dose: 16/sex in control; 26/sex in treated
Doses: 4, 12, 40 and 60 mg/kg/day
Duration: 13 weeks

Mortality: One male in the HD, considered unrelated to treatment.

Clinical signs: None attributable to treatment.

Bodyweight: There was a significant decrease in bw gain in males at the LMD, HMD and HD. There was a slight, and nonsignificant decrease in bw gain in females.

Food consumption: There was a significant decrease in fc in males at the HD only.

Biochemistry: No treatment related changes.

Organ weights: There was a dose-related increase in relative lung weights for all treated males and females which was statistically significant starting at the LD. Group mean relative liver weights were increased for females.

Macroscopic Pathology: Dose related increase in lung congestion.

Histopathology: Increased incidence of lung congestion in the two highest dose gps.

Toxicokinetics: Hamsters were studied to determine if they would be a suitable species for carcinogenicity testing since rats metabolize tolterodine differently than humans. DD01 was not produced to a great extent in hamsters but at the 60 mg/kg dose, serum DD01 levels (AUC) were

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39.4 (males) and 47.6 (females) ug.h/l. The concentration of DD01 was about 20% of the concentration of the parent tolterodine. Apparently the sponsors felt that this metabolite pattern was not sufficiently different from the rat to warrant use of the hamster in the carcinogenicity studies.

Toxicity to mice by repeated oral administration for 26 weeks followed by an 8-week recovery period.

Testing facility:
Study number: Pharmacia document 21744F
Date: 1994
Species/strain: CD-1(ICR)BR mice
Route: Oral gavage
Number/sex/dose: 30; a subgroup of 9-10 were sacrificed after 13 wks. Another gp of controls (9-10) and high dose (5-6) were treated for 26 wks then maintained for a recovery period. An additional 56/sex were treated at each dose and used for toxicokinetic sampling.
Doses: 3, 10 and 30 mg/kg
Duration: 26 weeks

Mortality: There was an increase in mortality in the high dose. Death occurred within a short time after dosing most within 1 hr. These animals had previously not shown any effects of treatment and there were no consistent abnormalities to account for the deaths and no cause of death was identified pathologically. The sponsor considers the deaths to be the result of the pharmacological action of the drug. Four HD animals died with convulsions which was considered treatment related.

Clinical signs: Convulsions prior to death in a few HD animals.

Bodyweight: Decrease in BW gain in HD females.

Food consumption: No effect.

Water consumption: Increase in water consumption in HD males and females.

Ophthalmoscopy: No effects.

Hematology: Slight but statistically significant reductions in PCV and Hb were seen for all treated female gps in comparison to controls. A decrease in PCV alone was noted for HD males. Associated with these changes were minor reductions in MCV for MD and HD animals, and increases in MCHC for HD mice. These changes were not seen after the recovery period.

Clinical chemistry: At 14 weeks, there was a slight but significant increase in BUN for MD and HD males and females and for LD males. At 26 wks, BUN was elevated in MD and HD females compared to controls but the control values were unusually low.

Urinalysis: Slight decrease in urine osmolality and sp gravity for MD and HD males. Reduction in urinary protein in HD males. Also seen in females but not significant. No differences were apparent after the recovery period.

Organ weights: Increased lung wt for HD males, increased adrenal wts for HD females and reduced liver wts for all treated female gps. All changes were reversed during recovery.
Gross path: Thickened uterus in HD females at wk 13 but not at wk 26.

Histopath: Liver - Increased incidence of centrilobular hepatocyte enlargement in HD males.

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No other toxicologically significant findings were noted, including the cause of the excess deaths in the HD animals.

Summary of toxicology:

Carcinogenicity:

24-Month Dietary Carcinogenicity Study in Mice.

Testing facility:
Study number: N583-Q1345
Date: 1996
Species/strain: :CD-1 BR mice
Route: Oral; mixed with diet
Number/sex/dose: 60; Satellite groups of 16 were used only for determination of systemic exposure to tolterodine and its metabolite DD01.
Doses: 0, 0, 5, 15 and 30 mg/kg
Duration: 24 months.

Because of the high mortality rate observed in male mice given the MD and HD, (54% and 74%, respectively, after 76 wks of dosing), all male gps were terminated on week 79. Females were sacrificed after 24 months of study.

Mortality: Progressive dose-related mortality was observed in males given 15 and 30 mg/kg/day starting from week 41 of study. The mortality rate reached an incidence of 55% and 78% beginning at wk 78, compared to a 20% mortality rate in the control gps. No substantial differences in mortality were seen in treated females compared to controls except for a slightly higher rate in HD females (63% vs 47% in controls after 2 yrs.). The main causes of death were due to a marked distention of the large intestine due to an abnormal presence of feces and less frequently to a dilatation of the urinary bladder with marked urine retention. These effects are considered to be related to the exaggerated antimuscarinic activity of the compound.

Body weight: A slight to moderate dose-related decrease in bw gain was noted in MD and HD males and females. The mean bw of MD and HD males were about 5% and 15% lower than controls at wk 77. The MD and HD females weighed approximately 5% and 10% less than controls starting at wk 57 and these differences persisted until the end of the study (7% and 12%, respectively, on day 720).

Food consumption: Although the sponsor states that there was not a significant effect on food consumption, the data indicate that there was a slight dose related reduction in food intake for both males and females. It may be enough to explain the decrease in body weight in the treated animals.

Systemic Exposure

Dose mg/kg	week	Tmax (hrs. of the day)		Cmax (ng/ml)		AUC t+20h (ngxhr/ml)	
		M	F	M	F	M	F
	tolterodine						
15	3	24	20	11	7.3	159	92
15	47	24	20	8.7	6.1	121	78
15	78(M)/100(F)	16	20	13	9.4	180	120

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30	3	8	8	35	19.6	445	277
30	47	4	20	23.3	24.2	322	347
30	78(M)/100(F)	24	24	43	35.4	367	375
	DD01						
15	3	4	20	6.3	5.2	107	80
15	47	24	20	6.9	5.7	110	84
15	78(M)/100(F)	20	20	6.7	6.3	107	86
30	3	8	8	16	13	235	193
30	47	4	20	13.5	16	209	253
30	78(M)/100(F)	16	24	8.6	12	129	171

The 5 mg/kg dose group had too few measurable concentrations to allow for pharmacokinetic calculations. Blood samples were taken from satellite animals at weeks 3, 47 and 78 (males)/100 (females).

Hematology: A minimal treatment-related anemia was seen in most HD males at wk 79. Possible decrease in leukocytes was seen in MD and HD males.

Clinical chemistry: No toxicologically significant changes.

Macroscopic pathology: Intestinal tract: In both MD and HD males and females there was distention of all three levels of the large intestine in those animals that died.

Microscopic pathology: Non-neoplastic lesions: Effects on intestinal tract and urinary bladder (dilation). Neoplastic lesions; No statistically significant dose tumor trends were detected in male or female mice.

24-Month dietary Carcinogenicity Study in Rats.

Testing facility:
Study number: N576-Q1342
Date: 1996
Species/strain: Sprague-Dawley CD(SD)BR rats
Route: Oral; mixed with diet
Number/sex/dose: 60; Satellite groups of 12 were used only for determination of systemic exposure to tolterodine and its metabolite DD01.
Doses: Males; 0, 0, 5, 15 and 30 mg/kg. Females 0, 0, 5, 10 and 20 mg/kg.
Duration: 24 months.

Mortality: No significant difference in mortality was seen between controls and treated animals of either sex. After 2 yrs the incidence of mortality in controls was 36% in males while it ranged from 43% to 52% in females. In treated gps the mortality rate ranged from 28% to 43% in males and from 43% to 60% in females without a dose relationship in either sex. Deaths in some incidences was due to distention of the large intestine due to an abnormal presence of feces.

Body weight: a dose-related decrease in bw gain, compared to controls, was observed at the MD and HD in both sexes. In males the bw gain was 20% to 35% less than controls at the end of the study. In females the decrease in bw gain was 28% and 44% in MD and HD, respectively, at the end of the study.

Food consumption: A 10% decrease in food intake was seen in HD males throughout the study. In females there was a 10% reduction in the MD and a 15% reduction in the HD compared to

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controls up to one year of treatment. After about week 76, the mean food intake in the MD and HD females was similar to that of controls.

Hematology: No treatment related changes.

Clinical Chemistry: No toxicologically significant changes.

Urinalysis: No treatment related changes.

Systemic Exposure: Tolterodine

Dose (mg/kg/day)	Week	Cmax (ng/ml)		AUC (ngxh/ml) t + 20h	
		Males	Females	Males	Females
5	3	0.53	0.27	4.2	—
5	53	0.41	0.64	6.0	7.4
5	103	3.9	2.2	44	23
15(M)/10(F)	3	1.3	1.2	20	17
15(M)/10(F)	53	3.9	6.3	42	95
15(M)/10(F)	103	74.9	4.8	764	70
30(M)/20(F)	3	3.2	16	44	217
30(M)/20(F)	53	97	28	623	388
30(M)/20(F)	103	73	17	718	269

Exposure to metabolite DD01 was negligible as no or very low serum levels of DD01 were detected.

Macroscopic Pathology: Intestinal tract; marked distention of the large intestine was seen in one LD male, two MD males and one MD female and nine males and seven females from the high dose group. This antimuscarinic effect was related to the deaths of these animals and the intestinal distention also occurred in one MD male that survived to the end of the study.

Lungs: Increased incidence of abnormal colored areas was seen in HD males and females.

Histopathology: The changes noted macroscopically in the large intestine were obscured by autolysis.

Lungs: Increased incidence and severity of alveolar macrophages was seen in HD males which correlated with the colored areas seen macroscopically.

Neoplastic findings: There was a significant dose-tumor positive linear trend for malignant renal liposarcoma in male rats and for benign vaginal fibromas in females.

Immunotoxicology:

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Reprotoxicology:

The preliminary reproduction studies were sponsors summaries.

Preliminary segment I study in the male mouse

Experimental design
The influence of tolterodine upon reproductive function and fertility was assessed in a preliminary study in sexually mature male mice of the CD-1 strain.

Tolterodine was administered by gavage at dosages of 12, 20 or 40 mg/kg/day to groups of six or ten male mice for 15 days before pairing. Treatment of the males was continued until the untreated females had littered. After delivery the offspring were reared until day 4 after birth. Control males received the vehicle, water, throughout the same period.

Results

Three males, treated with tolterodine at a dosage of 40 mg/kg/day, exhibited postdosing piloerection during the first three days of treatment. With these exceptions, the general condition of the animals was similar in all groups. One male receiving 40 mg/kg/day was found dead after dose administration on the first day of treatment. Body weight and bodyweight gain of the males were unaffected by treatment with tolterodine.
Food intake of the males was unaffected by treatment.
Water intake of the males was slightly increased in the 40 mg/kg/day dosage group. Mating performance and fertility were unaffected by treatment.
Littering and litter parameters were unaffected by treatment of the parental males. Necropsy findings for the parents and their offspring did not reveal any changes considered to be attributed to treatment.

Conclusions

It was concluded from this dose range-finding study, in the male mouse, that dosages of tolterodine of up to 40 mg/kg/day, administered by oral gavage, should be suitable for use in a main fertility study in this strain of animal.

Preliminary segment I and III study in the female mouse

Experimental design
The influence of tolterodine upon reproductive function and fertility was assessed in a preliminary study in sexually mature female mice of the CD-1 strain.

Tolterodine was administered by gavage at dosages of 4, 12, 20 or 30 mg/kg/day to groups of six female mice for 15 days before pairing. Treatment of the females was continued throughout mating, gestation and lactation to Day 7 after birth. Control females received the vehicle, water, throughout the same period.

Results

The general condition of the parental females was similar in all groups and no deaths occurred. Body weight performance was slightly inferior in animals treated with 30 mg/kg/day, compared with the control group, during the last week of the gestation period.

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Food intake was slightly reduced in the 30 mg/kg/day treatment group from the second week of treatment compared with the control group. In the same treatment group water intake was decreased during the lactation period.
Estrous cycles, mating performance and fertility, and littering were unaffected by treatment.
The number of implantation sites, litter size and post-implantation survival index were reduced in females treated with 30 mg/kg/day compared with the control group. Other litter parameters were unaffected by treatment.
Necropsy findings for the parental females and offspring did not suggest any treatment-related findings.

Conclusion

It was concluded from this dose range-finding study, in the female mouse, that dosages of up to 20 mg/kg/day, administered by oral gavage, should be suitable for use in a main fertility study in this strain of animal.

Reproductive function and fertility study in the mouse (segment I).

Testing facility:
Study number: 94/KBH008/0389
Date: 1994
Species/strain: CD-1 mice
Route: oral gavage
Number/sex/dose: 40
Doses: Males: 3, 10 and 30 mg/kg/day. Females: 3, 10 and 20 mg/kg/day
Duration: Males: from 71 days before pairing until successful parturition. Females: from 15 days before pairing, throughout the mating period and during gestation and lactation. Up to 26 females from each gp were killed on day 17 of gestation for examination of uterine contents. The remaining females were allowed to give birth and rear their young to weaning at day 22 of lactation. The offspring were then examined for behavioral responses.

Clinical signs: None treatment related.

Mortality: Six total, 3 in HD group, one male found dead on day 2 with no abnormalities at necropsy. Death possibly due to pharmacological effect of drug. All other deaths unrelated to treatment.
Bodyweight: No effect in males. In females, bw gain was marginally less in HD from day 12 of gestation to birth when compared to controls.

Mating performance and fertility: No treatment effects.

Teratology phase; females killed on day 17 of gestation
Mean no. of corpora lutea was significantly decreased in HD females and as a result there was a decrease in the number of implantations and viable young. The number of early and total resorptions were higher in HD when compared to controls and as a consequence, the extent of post-implantation loss was greater but not statistically significant. Fetal weight in HD gp was slightly lower than controls but not significant and within control range and not thought to be due to treatment.

Fetal evaluation: No treatment related abnormalities.

Post-natal phase:

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No effect on gestation length, parturition, gestation index, general condition of offspring, litter size and survival, physical development, auditory and visual responses, locomotor activity, water maze performance and sex ratio.

Bodyweight of offspring: At day 1 of age, bodyweights of male and female offspring of HD gp were slightly lower than those of controls. Subsequent bodyweights and bw gain were also low in this gp compared to controls. No other gps were affected.

F1-F2 generation
No treatment related effects on any parameter.

A preliminary study of the effect of 2234 on pregnancy of the mouse

Experimental design

In this preliminary assessment of the effect of tolterodine on pregnancy in the mouse, dosages of 0, 10, 30 and 90 mg/kg/day were administered orally to 12 female mice per group from Days 6 to 15 of pregnancy inclusive. On Day 17.5 the females were sacrificed, subjected to macroscopic post mortem examination, litter values determined and fetuses examined for gross abnormalities.

Results

In the parent females reduced bodyweight gain and slightly reduced food consumption were noted among dams given 90 mg/kg/day reflecting the lack of viable fetuses at this dose level. No effects of treatment on body weight gain and food consumption were noted among dams given 10 or 30 mg/kg/day.

Administration of 90 mg/kg/day resulted in total resorption of litters in all pregnant females. Administration of 10 or 30 mg/kg/day had no effect on the incidence of total resorption.

Among the surviving litters at termination there were reductions in mean fetal weight and total litter weight in the groups given 10 or 30 mg/kg/day in comparison with controls; however, no dosage-related trend was apparent. There was no indication of a treatment-related effect on the incidence of gross morphological changes noted.

Conclusions

Embryo viability was completely compromised among animals receiving 90 mg/kg/day. In addition mean fetal weights were reduced at both dosages where litters were produced (10 or 30 mg/kg/day). In view of these effects it is considered that further preliminary investigations are needed to establish suitable dosages for embryo-fetal toxicity studies.

Preliminary study of the effect of 2234 on pregnancy of the mouse

Experimental design

In this second preliminary assessment of the effect of tolterodine on pregnancy in the mouse, dosages of 0, 5, 15, 45 and 70 mg/kg/day were administered orally to 12 female mice per group from Days 6 to 15 of pregnancy inclusive. On Day 17.5 the females were sacrificed, subjected to macroscopic post mortem examination, litter values determined and fetuses examined for gross abnormalities.

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Results

In the parent females reduced bodyweight gain and slightly reduced food intake were noted among females given 70 or 45 mg/kg/day reflecting the lack of viable fetuses at these dose levels. No effects on body weight gain and food consumption were noted among females treated at 5 or 15 mg/kg/day.

Administration of 70 mg/kg/day resulted in total resorption of litters in all pregnant animals. Administration of 45 mg/kg/day resulted in total resorption of 2/10 litters, whereas no total litter loss was recorded in controls or females given 5 or 15 mg/kg/day.

Among surviving litters of dams given 45 mg/kg/day there were reductions in mean fetal weight and litter weight with clear increase in post implantation loss. There were no apparent adverse effects of treatment at 5 or 15 mg/kg/day. There was no indication of a treatment-related effect on the incidence of gross morphological changes noted.

Conclusion

There were clear effects on embryofetal parameters, embryo viability being completely compromised at 70 mg/kg/day and reduced at 45 mg/kg/day, with litter and mean fetal weights being reduced at 45 mg/kg/day. In view of the above, dosages of 45 mg/kg/day and above are considered unsuitable for a main embryofetal toxicity study.

The effect of Tolterodine on the pregnancy of the mouse following oral administration

Testing facility:
Study number: document 21037F
Date: 1993
Species/strain: CD-1 mice
Route: Oral gavage
Number/sex/dose: 30 females with 24 additional females used for toxicokinetic monitoring
Doses: 4, 12 and 40 mg/kg/day
Duration: From day 6 to day 15 of pregnancy

Clinical signs and mortality: No clinical signs. No treatment related deaths.

Bodyweight: Bodyweight gains in HD were lower than controls from day 10 of pregnancy with differences from controls attaining statistical significance. This was considered a consequence of the reduced litter weight.

Food consumption: No effects.

Gross pathology: None.

Litter data

A total of 1/25, 0/26, 1/24 and 9/29 pregnant females (control to HD, respectively) resorbed their litters pre-term. The females that showed total resorption in control and LD had few implantations and showed weight loss from the start of treatment. These resorptions were considered coincidental since it is not unusual for females with only a few implantations to show total resorption.

For the HD females, 3 instances of resorption were similar to the two cases above. However, for the remaining 6, the number of implantations was higher and effects on bodyweight were often

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apparent at later stages of pregnancy. Late in utero deaths were apparent in 2 females. It was concluded that these resorptions were due to treatment although it is uncertain if there was an indirect effect on the dams or if there was a direct in utero effect upon the conceptus.

Litter size, embryonic losses and sex ratio

No obvious treatment effect on implantations (which generally occur prior to treatment), although the number of implantations were lower in the treated gps than in the controls.

In utero deaths

Category	Total number in Group			
All pregnant females	control	LD	MD	HD
Implantations	303	277	269	310
In utero deaths				
early	22	14	22	93
late	3	0	2	54
Females with live young				
Implantations	300	277	267	236
In utero deaths				
early	19	14	20	36
late	3	0	2	37

There was no effect on sex ratio

Litter and mean fetal weight

Litter and mean fetal weight were significantly reduced at the HD when compared to controls. There were no obvious treatment related effects at the lower doses.

Malformations, anomalies and variants

Number of affected fetuses per litter	Number of litters in group			
Malformation	control	LD	MD	HD
0	20	21	23	9
1+	4	5	0	11
Visceral anomaly				
0	19	24	19	13
1+	4	2	4	2
2+	1	0	0	4
Skeletal anomaly				
0	18	18	16	2
1+	3	5	4	10
2+	3	3	2	7

There was a clear increase in the number of litters with one or more fetuses with structural changes (malformations and anomalies) at the high dose.

At 40 mg/kg/day a higher number of fetuses were considered malformed, with principal changes attributable to treatment being:

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malformation	control	high dose
cleft palate	0	10
digital abnormalities	1	7
intra-abdominal hemorrhage	2	6
reduced ossification	8	17
irregular ossification of costal cartilage elements	1	10
fused/connected sternebrae	0	3
additional thoraco-lumbar vertebra	0	6

A preliminary study of the effect of 2234 on the pregnant and non-pregnant rabbit

Experimental design

This study was a preliminary assessment of the effect of tolterodine on the pregnant and non-pregnant rabbit. Eight animals were employed. The study was performed in two phases.

Phase I consisted of two non-pregnant female animals, treated via the oral route with single doses of 8, 24, 72 and 48 mg/kg on Days 1, 4, 7 and 10 respectively.

Phase II consisted of two non-pregnant female animals, treated via the oral route at a dosage of 12 mg/kg/day for 13 days, and four pregnant animals treated by subcutaneous injection at varying doses including 0.2, 1, 3 and 5 mg/kg according to the schedule below. Dosing of pregnant rabbits commenced on Day 6 of pregnancy and finished, in the surviving rabbit, on Day 18 of pregnancy.

Results

Phase I

8 mg/kg resulted in increased respiration in both rabbits and transient bodyweight loss and reduced food consumption in 1/2 rabbits.

24 mg/kg resulted in increased respiration, transient bodyweight loss and reduced food consumption.

72 mg/kg resulted in increased respiration and unsteady gait in both rabbits, dilated pupils, convulsions and death in 1/2 and dark eyes in the survivor. Transient bodyweight loss and reduced food consumption were noted in the survivor.

48 mg/kg resulted in increased respiration and dark eyes, transient bodyweight loss and continuous reduced food consumption up to sacrifice 5 days later.

There were no gross macroscopic pathological abnormalities considered to be related to treatment in either rabbit.

Phase II - non-pregnant rabbits
Treatment of 2 non-pregnant female rabbits with 12 mg/kg/day orally for 13 days resulted in no clinical signs or deaths, bodyweight loss for the first 2 days of treatment followed by fluctuating losses and gains, and reduced food consumption for the first 12 days of treatment. There were no gross macroscopic pathological abnormalities noted at necropsy and no abnormalities noted at histopathological examination of livers that were considered to be related to treatment

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Phase II - pregnant rabbits
Results of determination of parent drug serum levels following oral administration in Phase I of the study (data on file at the Sponsor) indicated that very low levels of parent drug were achieved. Thus it was decided to investigate the tolerance following a parenteral route of administration (subcutaneous).
Subcutaneous dosing of pregnant rabbits according to the following schedule gave these results:

Animal number	Dose level (mg/kg)	Days of pregnancy dosed	Findings
	1	6-8	Dilated pupils and increased respiration after all doses, convulsions and death after the third dose; bodyweight loss; reduced food consumption; no gross macroscopic abnormalities
	1	6	No clinical signs; bodyweight loss; no effect on food consumption.
	3	7, 8	Increased respiration; bodyweight loss; marked reduction in food consumption.
	0.2	11-18	Increased respiration after first dose only, then no clinical signs; no effect on bodyweight or food consumption.
	Sacrificed Day 29		No gross macroscopic abnormalities in dam or pups attributable to treatment. No effect on litter parameters attributable to treatment.
5		6	Increased respiration, dilated pupils, dark eyes, found dead. No post dosing bodyweight or food consumption data available. No gross macroscopic abnormalities.
5		6	Increased respiration, dilated pupils, dark eyes, 1 convulsion; marked bodyweight loss and reduced food consumption.

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3	7	Increased respiration, 3 convulsions, died following third convulsion; No post-dosing bodyweight or food consumption data available; no gross macroscopic abnormalities attributable to treatment.

Overall, the spectrum of clinical signs noted was typical of those associated with the anticholinergic activity of the compound. The deaths were also likely to have resulted from this pharmacological effect. At sub-lethal doses, reduced growth and food consumption indicated that treatment with the test compound was compromising the health status of the animals. However no treatment-related macroscopic pathological change was evident in any of the animals.

Conclusions

The dose range finding for oral administration carried out as Phase I of this study enabled the selection of 12 mg/kg/day as a dose level for repeated administration. This dosage level in non-pregnant female rabbits produced initial bodyweight loss and reduced food consumption. It is considered that the highest oral dose that should be given to pregnant rabbits is in the region of 12 mg/kg/day.

Subcutaneous doses of 1, 3 and 5 mg/kg resulted in death and are clearly unsuitable for further investigation. A dose level of 0.2 mg/kg/day subcutaneously from Days 11 to 18 of pregnancy had no substantial adverse effects. It is considered that a high dosage level of above 0.2 but less than 1 mg/kg/day would be suitable for further investigation of the effects of tolterodine by the subcutaneous route in the pregnant rabbit.

A preliminary study in the pregnant rabbit with 2234 by gavage together with toxicokinetic monitoring.

Experimental design

In this preliminary assessment of the effect of tolterodine on pregnancy in the rabbit, dosages of 0, 4, 8 and 15 mg/kg/day were administered orally to 8 rabbits per group from Days 6 to 18 of pregnancy inclusive. On Days 6 and 16 samples were obtained for serum drug level analysis. On Day 29 the animals were sacrificed, subjected to a post mortem examination, litter values determined and fetuses examined for gross abnormalities.

Results

In the parent females increased respiration was observed post-dosing on the first two days of treatment in a few animals receiving 8 or 15 mg/kg/day. A reduction in food intake was noted at 15 mg/kg/day.

No treatment-related effect on body weight gain was noted.

There were no adverse effects of treatment of the litter parameters assessed.

Analysis of serum concentrations of tolterodine on days 6 and 16 of pregnancy showed a mean peak serum level (Cmax) of 1.5 ug/l after treatment with 4 mg/kg/day. After treatment with 8 mg/kg/day the mean Cmax value was about 2 ug/l and at 15 mg/kg/day the corresponding value was about 6 ug/l. Estimation of the area under the serum concentration curve (AUC) for

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tolterodine showed values of about 5 ugxh/l after 4 mg/kg/day, 9 ugxh/l after 8 mg/kg/day and 25 ugxh/l after 15 mg/kg/day. Analysis of the hydroxylated metabolite of tolterodine (DD01) showed mean peak serum levels of about 1 ug at 4 mg/kg/day and 1-2 ug/l at 8 mg/kg/day. After treatment with 15 mg/kg/day the mean Cmax value was about 6 ug/l. AUC values for DD01 were about 5, 8 and 20 ugxh/l for the three dosage levels.

Conclusions

In the parent females post-dosing clinical sign and reduced food intake were recorded at 15 mg/kg/day. There were no effects of treatment on embryofetal parameters. In view of the above a dosage in the region of 15 mg/kg/day is considered a suitable top dosage for an ensuing embryo-fetal toxicity study using the oral route.

A preliminary study in the pregnant rabbit with 2234 by subcutaneous injection together with toxicokinetic monitoring

Experimental design

In this preliminary assessment of the effect of tolterodine on pregnancy in the rabbit, dosages of 0, 0.2, 0.45 and 0.9 mg/kg/day were administered via subcutaneous injection to 8 rabbits per group from days 6 to 18 of pregnancy inclusive. On days 6 and 16 samples were obtained for serum drug level analysis. On day 29 surviving animals were sacrificed, subjected to a post mortem examination, litter values determined and fetuses examined for gross abnormalities.

Results

In the parent females, one rabbit given 0.9 mg/kg died following the first dose. Also, weight losses and reduced food intake were noted on the first two days of treatment at 0.9 mg/kg/day.

Weight loss over the first 2 days of treatment and reduced food intake for the first 8 days of treatment were noted at 0.45 mg/kg/day and reduced weight gain over the first 2 days of treatment only at 0.2 mg/kg/day.

There were no adverse effects of treatment on the litter parameters assessed.

Analysis of serum concentrations of tolterodine on days 6 and 16 of pregnancy showed a mean peak serum level (Cmax) of about 10 ug/l after treatment with 0.2 mg/kg/day. After treatment with 0.45 mg/kg/day the mean Cmax value was about 20 ug/l. At 0.9 mg/kg/day the mean Cmax value was about 40 ug/l. Estimation of the area under the serum concentration curve (AUC) for tolterodine showed values of about 25 ugxh/l after 0.2 mg/kg/day and about 110 ugxh/l after 0.9 mg/kg/day. Analysis of the hydroxylated metabolite of tolterodine (DD01) showed mean peak serum levels of 0.7 ug/l at 0.2 mg/kg/day and 1.3 ug/l at 0.45 mg/kg/day. After treatment with 0.9 mg/kg/day the mean Cmax value was about 4 ug/l. AUC values for DDO 1 were about 6 ugxh/l at 0.2 mg/kg and 20 ugxh/1 at 0.9 mg/kg/day.

Conclusions

One treatment related death occurred after dosing at 0.9 mg/kg. In the parent females at all dosages of tolterodine (0.2, 0.45 and 0.9 mg/kg/day) there was a transient initial adverse effect on body weight gain.
There were no effects of treatment on embryofetal parameters.
A dose level slightly below 0.9 mg/kg/day is considered suitable for an ensuing embryo-fetal toxicity study using the subcutaneous route.

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A study of the effect of tolterodine on pregnancy of the rabbit following subcutaneous administration.

Testing facility:
Study number: document 21036F
Date: 1993
Species/strain: New Zealand White Rabbits
Route: subcutaneous injection
Number/sex/dose: 16 females/dose
Doses: 0.2, 0.4 and 0.8 mg/kg/day
Duration: From day 6 to day 18 of pregnancy.

Clinical signs and mortality: One HD rabbit was found dead 2 hrs after dosing on the third day of treatment. Post mortem exam did not reveal the cause of death but the sponsor considered it treatment related.

Bodyweight: Initial treatment related bodywt loss of -2, -16 and -17 g compared to a +12 in the control gp by day 8. This was not statistically significant and was not sustained.

Food consumption: Statistically significant reduction in food intake at the HD during first few days and consumption remained slightly less until day 13 of pregnancy. Following cessation of treatment on day 18, food consumption of these rabbits was greater than that of controls from day 19 to day 28.

Terminal sacrifice: No differences noted.

Litter parameters

No obvious treatment related effects on the number of corpora lutea, implantation losses, type and distribution of embryonic deaths, live young, litter weight, mean pup weight and sex ratio.

Malformations, anomalies and skeletal variants

A slightly higher percentage incidence of gross/visceral anomalies was noted in HD rabbits (13.2%) in comparison with controls (5.8%) although this difference was not statistically significant. This was due to a greater incidence in the HD of anomalous cervico-thoracic arteries or abnormal lung lobation. The sponsor states that the incidence of anomalous cervico-thoracic arteries was within the control background range (6/116 fetuses affected in this study compared to a range of 0/109 to 10/112 in controls of 13 studies conducted around the same time). The anomalous lung lobes was above control background range (4/116 compared to 0/277 to 2/145) in the same 13 studies but the sponsor dismisses the result since 3 out of 4 of the affected fetuses were in the same litter and the number of litters affected was similar to the background range (2/14 compared to 0/31 to 2/18).

Note: For the anomalous cervico-thoracic arteries, need to know the historical range for the number of litters affected since in this study there were 2/16, 2/14, 4/16 and 6/14 in the control, LD, MD and HD respectively. There were no increase in cleft palate or any of the visceral or skeletal anomalies seen in mice.

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Genotoxicology: Sponsor's summaries

Study to determine the ability of tolterodine to induce mutation in two tryptophan requiring strains of Escherichia coli.

Tolterodine was assayed for mutation in 2 tryptophan-requiring strains (WP2 pKM101 and WP2 uvrA pKM101) of Escherchia coli, both in the absence and presence of metabolic activation by an induced rat liver post-mitochondrial fraction (S-9), In 2 separate experiments.
Experiment 1 treatments were carried out with both test strains, using final concentrations of tolterodine at 8, 40, 200, 1000 and 5OOO ug/plate plus a solvent and positive control. These treatments resulted in toxicity to strain WP2 uvrA pKM101 at 5OOO ug/plate, with further evidence of toxicity, in the form of a thinning of the background bacterial lawn, at 1000 ug/plate. 5OOO ug/plate treatments of strain WP2 PKMIOI produced varying signs of toxicity, but in all cases some evidence of toxicity was observed.
For Experiment 2, the maximum test treatments for strains WP2 pKMI01 and WP2 uvrA pKMI01 were reduced to 25OO and 1000 mg/plate respectively, these doses being estimates of the limits of toxicity for the 2 strains. For each strain a narrowed dose range was utilized in order to more closely examine those doses which were most likely to exhibit a mutagenic response. Experiment 2 treatments in the presence of S-9 also incorporated a pre-Incubation step, and in this way It was hoped to increase the range of mutagenic chemicals that can be detected using this assay system. Following Experiment 2 treatments evidence of slight toxicity, in the form of a thinning of the background bacterial lawn, and/or a marked reduction in reverent numbers below that of the solvent control treatments, was observed on all plates treated at the maximum done for each strain.
Negative (solvent) and positive control treatments were included for all strains In both experiments. The mean numbers of reverent colonies on negative control plates all fell within acceptable ranges, and were significantly elevated by positive control treatments.
Following treatments of the test strains In the absence and presence of metabolic activation (S-9), no statistically significant or dose related increases in reverent numbers were observed. This study therefore provided no evidence of tolterodine mutation induction.

It Is concluded that tolterodine was unable to induce mutation in 2 strains of Escherichia coli, when tested at concentrations up to the limit of toxicity In both the absence and presence of a rat liver metabolic activation system.

Study to determine the ability of tolterodine to induce mutation in four histidine-requiring strains of Salmonella typhimurium.

Tolterodine was assayed for mutation in four histidine requiring strains (TA98, TA100, TA1535 and TA1537) of Salmonella typhimurium, both in the absence and presence of metabolic activation by an induced rat liver postmitochondrial fraction (S-9), in two separate experiments.
An initial toxicity range-finder experiment was carried out in TA100 only, using final concentrations of tolterodine at 8, 40, 200, 1000 and 5000 ug/plate plus a solvent (dimethyl sulphoxide) and positive control. Complete toxicity was observed at 5000 ug/plate in the absence and presence of S-9. In experiment 1, therefore, the top test dose was reduced to 2500 ug/plate for all treatments, with a five-fold dilution series again providing the remaining doses. Despite these alterations, some toxicity was observed at 2500 ug/plate with strains TA98 and TA1535 in the absence of S-9, and both in the absence and presence of S-9 with TA1537. In the light of experiment 1 results, in experiment 2 the top dose for treatments in the absence of S-9 was reduced to 2000 ug/plate, whilst the top dose for treatments in. the presence of S-9 was maintained at 2500 ug/plate. In addition to these alterations, narrowed dose ranges were utilized in experiment 2 in order to investigate more closely those concentrations of tolterodine most likely to exhibit a mutagenic response. Following experiment 2 treatments, some signs of toxicity were again observed

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following top dose treatments of strains TA98, TA100 and TA1537 in the absence of S-9, and of strains TA100 and TA1535 in the presence of S-9.
Negative (solvent) and positive control treatments were included for all strains in both experiments. The mean numbers of reverent colonies on negative control plates all fell within acceptable ranges, and were significantly elevated by positive control treatments.
No treatment of any of the four test strains induced a significant increase in reverent numbers. In no case was there a two-fold (TA98 and TA100) or three-fold (TA1535 and TA1537) increase in reverent numbers that would normally be sufficient for a clear induction of mutation in these strains.

It is concluded that tolterodine was unable to induce mutation in four strains of Salmonella typhimurium, when tested up to concentrations toxic to the test bacteria in the absence and presence of a rat-liver metabolic activation system.

Study to evaluate the chromosome damaging potential of tolterodine by its effects on cultured human lymphocytes using an in vitro cytogenetics assay.

Tolterodine was tested in an in vitro cytogenetics assay using duplicate human lymphocyte cultures from a single female donor. Treatments were performed both in the absence and presence of metabolic activation by a rat liver postmitochondrial fraction (S-9) from induced animals. The test compound dose levels for analysis were selected by determining mitotic indices from a broad range of doses up to 1700 ug/ml, a concentration which induced toxicity and which was close to the maximum achievable practically using dimethyl sulphoxide as solvent. The top dose considered suitable for analysis, 466.9 ug/ml, induced approximately 55% and 81% mitotic inhibition in the absence and presence of S-9 respectively. The doses analyzed for chromosome aberrations were 197.2, 303.5 and 466.9 ug/ml. Appropriate negative (solvent) control cultures were included in the test system and contained low incidences of chromosomal aberrations within historical solvent control ranges. Methyl methanesulphonate (MMS) and cyclophosphamide (CPA) were employed as positive control chemicals in the absence and presence of liver S-9 respectively. Both compounds induced statistically significant increases in the incidence of chromosomal aberrations.
Treatment of cells in the absence and presence of S-9 resulted in numbers of structural aberrations which were similar to and not significantly different from those observed in concurrent solvent controls. Historical solvent control ranges for structural aberrations were not exceeded at any of the treatment doses analyzed. When gaps and/or numerical aberrations were included in the data, aberration frequencies in one culture treated with the intermediate dose and one culture treated with the low dose in the absence of S-9 exceeded historical control ranges. This was not considered to be of biological significance as increases were small and were not observed in the replicate cultures nor at the higher dose.

It is concluded that was unable to induce structural chromosome aberrations in cultured human lymphocytes when tested to its limit of toxicity in either the absence or presence of S-9.

Study to evaluate the chromosome damaging potential of tolterodine by its effects on cultured human lymphocytes using an in vitro cytogenetics assay.

Tolterodine was tested in an in vitro cytogenetics assay using duplicate human lymphocyte cultures from a male donor. The highest dose level used, 700 ug/ml was based on data generated in a previous assay on this chemical (above). Treatments covering a broad range of doses, separated by narrow intervals, were performed both in the absence and presence of metabolic activation by a rat liver post-mitochondrial fraction (S-9) from induced

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animals. Treatment in the absence of S-9 was continuous for 20 or 44 hours (20+0, 44+0). Treatment in the presence of S-9 was for 3 hours only followed by a 17 or 41 hour recovery period prior to harvest (3+17, 3+41). An additional treatment, in the absence of S-9, for 3 hours followed by a 17 hour recovery period was also performed.
The dose levels for analysis at each sampling time were selected by evaluating the effect of tolterodine on mitotic index. Chromosome aberrations were analyzed in cells receiving 20+0 hour treatments in the absence of S-9 and 3+17 hour treatments in its presence at 3 consecutive dose levels. The highest concentrations chosen for analysis were, 117.1 ug/ml (20+0, - S-9) and 505.8 ug/ml (3+17, + S-9), which induced approximately 67% and 63% mitotic inhibition respectively. The effects of single concentrations only, 99. 57 and 505.8 ug/ml (without and with S-9) were investigated at the delayed (44 hour) sampling time and following the 3+17 hour treatment in the absence of S-9 (429.9 ug/ml).
Appropriate negative (solvent) control cultures were included in the test system under each treatment condition. The proportion of cells with structural aberrations in these cultures fell within historical solvent control ranges. 4-Nitroquinoline 1-oxide (NQO) and cyclophosphamide (CPA) were employed as positive control chemicals following 20+0 hour treatments in the absence and 3+17 hour treatments in the presence of liver S-9 respectively. Both compounds induced statistically significant increases in the proportion of cells with structural aberrations.
In an initial experiment (consisting of 2 trials) several solvent control cultures were observed to have frequencies of cells with aberrations which exceeded historical solvent control ranges, thus data from this aborted experiment (both trials) are not reported here.
Treatment of cultures with tolterodine under most exposure conditions in the absence of S-9 resulted in frequencies of cells with chromosomes aberrations which were similar to and not significantly different from those in concurrent solvent controls. A small, but statistically significant increase in aberrations at the intermediate dose level scored following 20 hours of treatment was considered unlikely to be biologically significant insofar as it was not seen at the higher dose although mitotic inhibition (cell cycle delay) at both doses was similar.
Treatment of cultures in the presence of S-9 gave frequencies of aberrant cells which were significantly higher than those in concurrent controls at the low dose level scored following the 3+17 hour treatment (365.4 ug/ml) and at 505.8 ug/ml following the 3+41 hour treatment. These increases were not considered biologically significant because numbers of aberrant cells in all cultures fell within the normal range.

It is concluded that tolterodine was unable to induce chromosome aberrations in human lymphocytes when tested to its limit of toxicity in both the absence of and presence of S-9.

Study to determine the ability of tolterodine to induce mutations at the locus in mouse lymphoma L5178Y cells using a fluctuation assay.

Tolterodine was assayed for mutation at the locus (6-thioguanine resistance) in mouse lymphoma L5178Y cells using a fluctuation protocol. The study consisted of two independent experiments, each conducted in the absence and presence of metabolic activation by an induced rat liver post-mitochondrial fraction (S-9).
Following a wide range of treatments, separated by half-log intervals and reaching 2160 ug/ml, cells survived at 216 ug/ml yielding 26% relative survival in the absence and 83% relative survival in the presence of S-9. This dose, together with the next 4 lower doses, was plated for viability and 6-thioguanine resistance 7 days after treatment. In the second experiment a narrower dose range was used to maximize the chance of detecting any dose-related effects. The top doses plated in this experiment were 250 ug/ml and 500 ug/ml in the absence and presence of S-9, which yielded 69% and 3% relative survival respectively. In this experiment these and the next 3 (- S-9) or 4 (+ S-9)- lower doses were plated for determination of mutant frequency 7 days after treatment.

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Solvent (DMSO) and positive control treatments were included in each experiment in the absence and presence of S-9. Mutation frequencies in negative (solvent) control cultures fell within normal ranges, and statistically significant increases in mutation were induced by the positive control chemicals 4-nitroquinoline I-oxide (without S-9) and benzo(a)pyrene (with S-9).
In both experiments, no treatment with tolterodine, either in the absence or presence of S-9, resulted in a statistically significant increase in mutation frequency.

It is concluded that, under the conditions employed in this study, tolterodine failed to induce mutation at the locus of L5178Y mouse lymphoma cells when tested up to toxic concentrations, in the absence and presence of a rat liver S-9.

Study to evaluate the potential of tolterodine to induce micronuclei in the polychromatic erythrocytes of CD-1 mice.

Tolterodine was assayed in vivo in a mouse bone marrow micronucleus test at 3 dose levels. The choice of dose levels was based on an initial toxicity range-finder study in which tolterodine dissolved in distilled water was administered orally to 3 male and 3 female mice on 2 consecutive days at doses of 105.5, 140.6, 187.5 and 250 mg/kg. From the pattern of mortality the LD50 was estimated at approximately 217 mg/kg (x 2). For the micronucleus test tolterodine was dissolved in distilled water and administered orally as 2 daily doses at 37.5, 75 and 150 mg/kg to groups of 5 male and 5 female mice killed 24 or 48 hours after the second dose. Two animals receiving the highest dose died prior to sampling indicating that it would not have been practicable to administer the test chemical at a higher dose.
The negative (vehicle) control in the study was distilled water also administered orally on 2 consecutive days. Groups of 5 male and 5 female mice treated with this were killed and sampled 24 or 48 hours after the second dose. Cyclophosphamide (CPA), the positive control, was dissolved in water and administered orally as a single dose at 80 mg/kg to groups of 5 male and 5 female mice which were killed after 24 hours. All positive control animals exhibited increased numbers of micronucleated polychromatic erythrocytes (PCE) such that the micronucleus frequency in the positive control group was significantly greater than in the negative control group. Slides from all dose groups sacrificed after 24 hours, and slides from top dose and control groups sacrificed after 48 hours were analyzed. Negative (vehicle) control mice exhibited acceptable ratios of PCE to NCE (normochromatic erythrocytes) and normal frequencies of micronucleated PCE within historical negative control ranges. Mice treated with tolterodine at all doses and sampling times exhibited ratios of PCE to NCE and frequencies of micronucleated PCE which were similar to vehicle controls. There were no instances of statistically significant increases in micronucleus frequency for any of the groups receiving the test chemical at any sampling time.

It is concluded that tolterodine did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of mice treated on two consecutive days with doses up to 150 mg/kg, a dose at which limited mortality was observed.

Genotoxicology of DD01

The active metabolite DD01 was tested separately in in vitro tests using
and human lymphocytes with and without a S-9 metabolizing system. The results were negative.

Special toxicology studies:

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OVERALL SUMMARY

Tolterodine is a competitive muscarinic receptor antagonist. It binds with high affinity and specificity to muscarinic receptors, as compared with other receptor types. It is more potent in inhibiting acetylcholine-induced urinary bladder contractions than electrically-induced salivation in vivo in anesthetized cats.

Tolterodine has been adequately tested in mice, rats and dogs. Most of the effects seen were the result its antimuscarinic actions. There was increased motor activity, mydriasis, decreased intestinal motility, development of residual urine and increased heart rate. Some dogs given 4.5 mg/kg showed ataxia, sedation and sensitivity towards light and trembling. In these dogs, there was a higher frequency of keratitis and/or corneal opacities and conjunctivitis compared to controls. The pupillary reflex was absent in some high dose dogs after 6 and 12 months of dosing. Tolterodine produced increased heart rate in dogs even at the lowest (0.5 mg/kg) dose which means a no-effect dose has not been identified. A decrease in the PQ-interval was seen in both sexes primarily in dogs receiving 1.5 and 4.5 mg/kg/day. The QRS-interval was unchanged. Changes in the QT-interval probably reflect the increase in heart rate although there was an increase in the QTc interval as well. Drug blood levels (AUC) in these dogs were approximately 10 to 150 times higher than drug blood levels in people taking 2 mg bid. There were unexplained deaths in the mouse carcinogenicity studies at the highest dose. A telemetry study in mice using high doses did not reveal any cardiovascular effects. Doses in the mouse carcinogenicity study produced drug blood levels approximately 10 times higher that the drug blood levels in humans taking 2 mg bid. Free drug blood levels were approximately 45 times higher in mice than in humans.

Little or no target organ toxicity (other than the pharmacodynamic effects noted above) were produced by tolterodine. Some mild liver changes were seen in rats and dogs and increased incidence and severity of alveolar macrophages were seen in the lungs of rats.

Tolterodine has some structural similarities to terodiline which was withdrawn from the market due to suspected associations with cardiac events, particularly Torsades de Pointes and QTc prolongation. Tolterodine does prolong the QTc in dogs and the sponsor was asked to do a 52 week study in dogs to examine the effect of tolterodine on the ECG. Tolterodine increased heart rate in dogs sporadically even at the lowest dose so no no effect dose was identified. A decrease in the PQ-interval was seen in both sexes primarily after treatment with 1.5 and 4.5 mg/kg (drug blood AUC's approximately 10 to 150 times higher than drug blood AUC's in humans taking 2 mg bid). This safety margin decreases to a minimum of 7.6 if tolterodine and DD 01 (the major active metabolite) are combined comparing humans on 2 mg bid vs female dogs receiving 1.5 mg/kg. The minimum margin of safety decreases to 4.2 if free tolterodine plus free DD 01 are compared between humans and dogs. Furthermore, the no effect dose of 0.5 mg/kg produces minimum drug multiples of 3.7 for total tolterodine, 2.6 for tolterodine plus DD 01 and 1.3 for free tolterodine plus free DD 01. Thus the drug exposure level that produced an increased PQ interval may be only slightly greater than the average drug exposure in humans taking 2 mg bid. These multiples of the human exposure are for extensive metabolizers of tolterodine. For poor metabolizers, the drug blood levels will be well above the drug blood levels that cause changes in ECG in dogs. For example, in clinical study 95-OATA-030, when given to extensive metabolizers, 2 mg bid tolterodine gave serum AUC values for tolterodine and DD01 of 62 ug.h/L. In the same study, 2 mg bid given to poor metabolizers resulted in no serum DD01 but an AUC of 216 ug.h/L for tolterodine. Thus the total pharmacologically active moieties are 3.5 times higher in poor metabolizers than in extensive metabolizers and the safety margin is lower by a similar amount.

In the pharmacology safety studies, an iv dose of 0.06 mg/kg to anesthetized dogs (serum levels of 45-87 ng/ml) produced a 6-8% increase in QT, QTc intervals and T-wave amplitude and duration. Doses producing serum tolterodine levels of 398-1510 ng/ml produced a 30% increase

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in QT interval, 20% increase in the QTc interval and a 40% increase in the T-wave duration. Following oral administration, there was no change in ECG until serum tolterodine levels reached over 600 ng/ml (increase in the QT interval of approximately 10-20%). In anesthetized cats, tolterodine decreased the T-wave amplitude at serum concentrations of 188 ng/ml and above. The Cmax in humans taking 2 mg bid is approximately 3.6 ng/ml tolterodine.

There were unexplained deaths in the mouse carcinogenicity study at the high dose of 30 mg/kg/day. These doses resulted in drug blood level multiples of 10.4 for tolterodine, 8.9 for tolterodine plus DD 01 and 17.6 for free tolterodine plus free DD 01. For the next lower dose (the dose that had no increase in mortality) the drug blood level multiples were 3.7 for tolterodine, 3.6 for tolterodine plus DD 01 and 7.8 for free tolterodine plus free DD 01.

If cardiac toxicity's are the result of acute high blood levels of drug (Cmax) then the margin of safety is greater for dogs (26 for tolterodine, 18 for tolterodine plus DD 01 and 8.5 for free tolterodine plus free DD 01). However, for mice, the margin of safety decreases to 11 for tolterodine, 2.2 for tolterodine plus DD 01 and 4.5 for free tolterodine plus free DD 01.

Based on the drug blood multiples between animals and humans, there is not much margin of safety for cardiovascular events. For slow metabolizers of tolterodine, there probably is no margin of safety. Because tolterodine has structural similarities to a previous drug that was withdrawn from the market for possible cardiac effects such as Torsades de Pointes and QTc prolongation, and because tolterodine has similar cardiac effects in animals at fairly low doses, the risk to benefit ratio for tolterodine would seem to be small. However, tolterodine is much more specific for the muscarinic receptor than is terodiline which cross reacts with histamine and alpha-adrenergic receptors and calcium channels. Furthermore, the serum levels of tolterodine at a therapeutic dose are significantly lower than the serum levels of terodiline so the overall safety margin would seem to be much greater for tolterodine than for terodiline.

Electrophysiology studies in isolated cardiac tissue also demonstrated an adequate safety margin for tolterodine. Significant effects on cardiac calcium and sodium channels occurred at concentrations well above those seen in humans taking 2 mg bid. However, this margin of safety will be reduced by approximately one-third in poor metabolizers.

In the rat carcinogenicity study there was a significant increase ($p<0.025$) in malignant renal liposarcoma in males only. The actual numbers were 0/60 control 1, 0/60 control 2, 1/60 LD, 1/60 MD and 3/60 HD. This is a rare tumor with the historical incidence in the lab that did the study ranging from 0 to 1.6% (although the lab has done only a small number of carcinogenicity studies). The 5% incidence in the HD is above the historical control value but the effect was not seen in female rats or male or female mice. Because tolterodine was negative in a large battery of genotoxicity tests the mechanism of carcinogenicity (if the effect is real) is probably epigenetic in nature. The high dose in the rat carcinogenicity study of 30 mg/kg in males results in drug blood levels of tolterodine approximately 13.6 time higher than the drug blood levels in humans taking 2 mg bid. This margin of safety decreases to 7.5 for tolterodine plus DD 01 and to 9.4 for free tolterodine plus free DD 01. However, it is possible that the carcinogenic dose is only slightly above the mid-dose group. In that case the multiples will be significantly lower.

The negative genotoxicity, the weak carcinogenic signal (one sex, one species) and the approximately 10 fold higher drug blood levels in male rats than in humans provides sufficient evidence to consider tolterodine as extremely unlikely to produce cancer in humans. Again, slow metabolizers of tolterodine could be at a higher risk.

There was no effect on fertility (percent of females pregnant) in mice given 30 (M) or 20 (F) mg/kg tolterodine, but there was a reduced number of corpora lutea resulting in fewer implantation sites and fewer viable young. There was also an increased number of early and late resorptions in

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these mice. Teratology studies with tolterodine provided evidence that drug treatment can increase the incidence of malformations. In mice there was an increase in cleft palate, digital abnormalities, intra-abdominal hemorrhage and various minor skeletal variations, primarily reduced ossification. In rabbits, tolterodine treatment produced an increase in gross/visceral abnormalities due primarily to an increase in anomalous cervico-thoracic arteries.

RECOMMENDATIONS

Internal comments: From the standpoint of Pharmacology, Detrusitol can be approved for the treatment of patients with overactive bladder.

External recommendations (to sponsor): None

NDA issues: None

Labeling review: Some minor modifications of the label may be necessary.

Investigator's brochure/Informed consent review:

Reviewer signature/Team leader signature: /S/ 12/22/97

CC list: HFD-580

Appendix:

Draft date:

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-771

STATISTICAL REVIEW(S)

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0110

Dickson

STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)

NDA #: 20-771 NOV 19 1997

APPLICANT: Pharmacia & Upjohn Company

NAME OF DRUG: DETRUSITOL™ (Tolterodine Tablets)

DOCUMENTS REVIEWED: Volumes 1.35 &1.38 (Mouse Study) and 1.39 &1.43 (Rat Study) of NDA 20-771. Data on floppy diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Alex Jordan, Ph.D. (HFD-580).

I. BACKGROUND

In this NDA submission, two animal carcinogenicity studies (P9359 in mice and P9350 in rats) were included. These two studies were conducted to obtain information on the carcinogenicity of Detrusitol when given to CD-1 mice and Sprague Dawley rats in the diet for two years.

II. THE MOUSE STUDY (P9359)

IIa. Design

Detrusitol was administered to 60 CD-1 mice/sex/group in concentrations of 0 (control 1), 0 (control 2), 5 (low), 15 (medium) and 30 (high) mg/kg/day in the diet for two years. Two control groups/sex received the untreated diet.

The female mice were treated for 24 months whereas all male mice groups were terminated from week 79 because of high mortality in them for the medium and high doses.

IIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the papers by Cox (1972) and Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics II. The results are included in the Appendix.

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Survival Analysis: The purpose of the survival analysis was two-fold:
(1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
(2) To determine the significance of a positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al. (1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 1a, 1b, 2a and 2b summarize the intercurrent mortality data for the male and female mice respectively. For the male mice, in the time-intervals of 0-52 and 53-78 weeks, there appears to be an increased mortality in the medium and high dose groups as compared to other dose groups (see Figure 1a in the Appendix). For the female mice, in the time-interval of 79-91 weeks, more animals died in the high dose group than in other dose groups (see Figure 1b in the Appendix).

- Figures 2a and 2b depict the Kaplan-Meier survival distributions for males and females respectively. For the male mice, at 79 weeks, there appears to be an increased mortality in the medium and high dose groups when compared to the other doses. For the female mice, the curves for different dose groups (except the high dose group) intertwine each other suggesting that there is no significant difference between their survival patterns (except for the high dose group). Mortality is higher in the high dose group as compared to other groups for female mice. The test of homogeneity yields significant results for the male mice (Table 3a in the Appendix) and non-significant results for female mice (Table 3b in the Appendix).

- Table 3a and 3b display the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis (Gehan) test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test which gives equal weight to all deaths. For male mice, the test of homogeneity and the test of linear trend yield significant results which confirm the graphical findings of Figure 1a and 2a. For female mice, the Cox-test of linear trend yields significant results (p=0.0360) which confirm the graphical findings of Figure 1b and 2b.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of a positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal. Table 4 (Part I) displays selected organs and organ codes. Table 4 (Part II) displays tumors and tumor codes.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused

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death for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 0, 5, 15, and 30 for the control 1, control 2, low, medium, and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 0, 5, 15 and 30 mg/kg/day of Detrusitol. The time-intervals used were 0-52, 53-78, 79 and beyond for males and 0-52, 53-78, 79-91, 92-103, 104 and beyond for females.

The tumor analysis results are displayed in the Appendix. Tables 5a and 5b describe the p-values for the test of trend based on the tumor data. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types.

IIc. Evaluation of Validity of the Design of Mouse Study (P9359)

This reviewer's analyses show that for mouse study, there is no statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in mice, it is important to look into the following two issues as having been pointed out by Haseman (1984) in Environmental Health Perspective:

(i) Were enough animals exposed, for a sustained amount of time, to the risk of a late developing tumor?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the mice?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

(i) Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on average,

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approximately 50% of the animals in the high dose group survived the two-year study period.

(ii) Also, in personal communication with Dr. Karl Lin of Division of Biometrics II, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

(iii) In addition, Chu, Cueto and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy:

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the mouse carcinogenicity study in the light of the above guidelines.

Validity of Mouse Study (P9359)

Male Mice:

It appears that the high dose given to male mice probably exceeded the MTD of Detrusitol. While the study of male mice was planned as a 24-month study, because of the low survival in the high dose group, the study was terminated after 18 months.

The sponsor indicated that (p. 28, vol. 1.35) body weight for medium and high-dose males was respectively about 15% and 5% lower than controls at week 77. From the weight-gain criteria mentioned above, it can probably be concluded that the high dose used exceeded the maximum tolerated dose for the male mice. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

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By considering survival rates (subtracting mortality rates from 100% in Table 2a) for male mice for all the dose levels and for the times: end of 52 weeks, and end of 78 weeks, it can be concluded that enough numbers of male mice were exposed to the drug for a sufficient amount of time following the above-mentioned criterion of Chu, Cueto and Ward (1981).

Female Mice:

By considering survival rates (subtracting mortality rates from 100% in Table 2b) for female mice for all the dose levels and for the times: end of 52 weeks, end of 78 weeks, end of 91 weeks and end of 103 weeks, it can be concluded that enough numbers of female mice were exposed to the drug for a sufficient amount of time following the above-mentioned criteria.

The sponsor indicated that (p. 28, vol. 1.35) body weight for medium and high-dose females was respectively about 5% and 10% lower than that of controls starting from week 57. These differences persisted up to the end of study. From the weight-gain criteria mentioned above, it can be concluded that the high dose used may be close to the maximum tolerated dose for the female mice. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IId. Summary of Mouse Study (P9359)

The doses of Detrusitol appeared to adversely affect survival in mice. For male mice, a highly statistically significant dose-mortality trend was detected. That is, a clear trend of decreased survival with increased dose is evident. It appears that the high dose given to male mice probably exceeded the MTD of Detrusitol. For female mice, a marginally statistically significant (Cox p=0.0360, Kruskal-Wallis p=0.0537) dose-mortality trend was detected.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of mice were exposed to the drug for a sufficient amount of time in both sexes. From the weight-gain criteria, it can probably be concluded that the high dose used exceeded the maximum tolerated dose for the male mice. But for female mice, the high dose used may be close to the maximum tolerated dose. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

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III. THE RAT STUDY (P9350)

IIIa. Design

Detrusitol was administered to 60 Sprague-Dawley male rats/group in concentrations of 0 (control 1), 0 (control 2), 5 (low), 15 (medium) and 30 (high) mg/kg/day and 60 Sprague-Dawley female rats/group in concentrations of 0 (control 1), 0 (control 2), 5 (low), 10 (medium) and 20 (high) mg/kg/day in the diet for two years. Two control groups/sex received the untreated diet.

IIIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the papers by Cox (1972) and Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics II. The results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:
(1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
(2) To determine the significance of a positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al. (1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 6a, 6b, 7a and 7b summarize the intercurrent mortality data for the male and female rats respectively. For the male rats, in the time-intervals of 53-78 weeks, 79-91 weeks and 92-102 weeks, there appears to be an increased mortality in the low dose group as compared to other dose groups (see Figure 3a in the Appendix). For the female rats, in the time-interval of 79-91 weeks, there appears to be an increased mortality in the low dose group as compared to other dose groups; but in 92-102 weeks, there appears to be an increased mortality in the medium dose group as compared to other dose groups (see Figure 3b in the Appendix).

- Figures 4a and 4b depict the Kaplan-Meier survival distributions for males and females respectively. For the male rats, after 102 weeks, there appears to be an increased mortality in the low dose group when compared to the other doses. For the female rats, after 102 weeks, mortality is lowest in the high dose group and highest in the medium dose group. The test of homogeneity does not yield significant results for the male and the female rats (Table 8a and 8b in the Appendix).

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Table 8a and 8b display the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis (Gehan) test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test which gives equal weight to all deaths. The test of homogeneity and the test of linear trend do not yield significant results for the male and the female rats.

No statistically significant differences in survival were detected for male or female rats.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of a positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal. Table 9 (Part I) displays selected organs and organ codes. Table 9 (Part II) displays tumors and tumor codes.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused death for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. For male rats, the scores used were 0, 0, 5, 15 and 30 for control 1, control 2, low, medium, and high dose groups respectively. For female rats, the scores used were 0, 0, 5, 10 and 20 for control 1, control 2, low, medium, and high dose groups respectively. This was done in order to reflect the actual dose levels of Detrusitol. The time-intervals used were 0-52, 53-78, 79-91, 92-102, 103 and beyond for males and females.

The tumor analysis results are displayed in the Appendix. Tables 10a and 10b describe the p-values for the test of trend based on the tumor data. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types for female rats. But for male rats, the following significant linear dose tumor-trend was indicated.

The number of males with malignant tumor renal liposarcoma for the kidney(s) for various dose groups is described in the Table below (see the shaded region of Table 10a). Of the five tumors that were observed, all were fatal. Since none were found in the control group, this tumor was classified as a "rare tumor". The exact p-value of 0.0185 is less than the

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cut-off of 0.025 for rare tumors (as described above). The tumor occurrence rate increased from 0% in the control group (0/60) to 5% in the high dose group (3/60).

Male Rats			Tumor Rate					Trend Test
Organ	Tumor Name	Tumor Type	CTRL 1 N=60	CTRL 2 N=60	LOW N=60	MED N=60	HIGH N=60	p-value
Kidney(s)	Malignant Tumor Renal Liposarcoma	Fatal	0	0	1	1	3	0.0185

IIIc. Evaluation of Validity of the Design of Rat Study (P9350)

For male rats, a statistically significant positive trend was observed in kidney malignant renal liposarcoma tumors, so no discussion of the validity of study design is needed for male rats. But, this reviewer's analyses show that there is no statistically significant positive linear trend for female rats. So, a discussion of the validity of study design is needed for female rats.

Before drawing the conclusion that the drug is not carcinogenic in female rats, it is important to look into the following two issues as having been pointed out by Haseman (1984) in Environmental Health Perspective:

(i) Were enough animals exposed, for a sustained amount of time, to the risk of a late developing tumor?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the rats?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

(i) Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on average, approximately 50% of the animals in the high dose group survived the two-year study period.

(ii) Also, in personal communication with Dr. Karl Lin of Division of Biometrics II, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

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(iii) In addition, Chu, Cueto and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy:

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the female rats carcinogenicity study in the light of the above guidelines.

Validity of Rat Study (P9350)

By considering survival rates (subtracting mortality rates from 100% in Table 2b) for female rats for all the dose levels and for the times: end of 52 weeks, end of 78 weeks, and end of 91 weeks, it can be concluded that enough numbers of female rats were exposed to the drug for a sufficient amount of time following the above-mentioned criteria.

The sponsor indicated (p. 28, vol. 1.39) that a dose-related decrease in body weight gain, in comparison to controls, was observed at the intermediate and high doses. The sponsor stated that at the high dose of 20 mg/kg/day the decrease in body weight gain was about 28% starting from week 8 and reached about 44% at the end of the study (when compared to the controls). The sponsor further stated that at intermediate dose of 10 mg/kg/day body weight gain was about 21% lower starting from week 24 and about 28% lower at the end of the study (when compared to the controls). From the weight-gain criteria mentioned above, it can be concluded that the high dose used may be over the maximum tolerated dose for the female rats. But the high dose group had a slightly higher mortality when compared with the pooled data of the two controls. Based on the mortality data, it can be concluded that the high dose is close to the MTD. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

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IIId. Summary of Rat Study (P9350)

No statistically significant differences in survival were detected for male or female rats.

For male rats, the positive linear trend in kidney malignant renal liposarcoma is considered to be statistically significant.

For female rats, none of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of female rats were exposed to the drug for a sufficient amount of time. From the weight gain criteria, it can be concluded that the high dose used (20 mg/kg/day) may be over the maximum tolerated dose for female rats. But the high dose group had a slightly higher mortality when compared with the pooled data of the two controls. Based on the mortality data, it can be concluded that the high dose is close to the MTD. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IV. SUMMARY

Mouse Study (P9359)

The doses of Detrusitol appeared to adversely affect survival in mice. For male mice, a highly statistically significant dose-mortality trend was detected. It appears that the high dose given to male mice probably exceeded the MTD of Detrusitol. For female mice, a marginally statistically significant dose-mortality trend was detected.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups for both sexes when compared with the control.

From the survival criteria, it can be concluded that enough numbers of mice were exposed to the drug for a sufficient amount of time in both sexes. From the weight-gain criteria, it can probably be concluded that the high dose used exceeded the maximum tolerated dose for the male mice. But for female mice, the high dose used may be close to the maximum tolerated dose. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

Rat Study (P9350)

No statistically significant differences in survival were detected for male or female rats.

For male rats, the positive linear trend in kidney malignant renal liposarcoma is considered to be statistically significant.

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For female rats, none of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of female rats were exposed to the drug for a sufficient amount of time. From the weight gain criteria, it can be concluded that the high dose used (20 mg/kg/day) may be over the maximum tolerated dose for female rats. But the high dose group had a slightly higher mortality when compared with the pooled data of the two controls. Based on the mortality data, it can be concluded that the high dose is close to the MTD. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

/S/

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Mathematical Statistician (Biomed)

Concur: Dr. Lin

11/19/97

/S/

cc: Archival NDA 20-771
HFD-580/Jordan, CSO, Division File
HFD-715/Taneja, Kammerman, Lin, Nevius, Division File, Chron.

There are total 53 pages (12 pages of text, 32 pages of tables, 8 pages of figures and 1 page containing references) in this review.

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APPENDIX

For tumor type MIXED, use asymptotic p-value.
For tumor type IN (INCIDENTAL), use exact p-value.
For tumor type FA (FATAL), use exact p-value.

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Table 1a

NUMBER OF ANIMALS DIED

Species: Mouse
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	1	6	4	10	18	39
53-78	4	9	11	23	27	74
79-81	55	45	45	27	15	187
Total	60	60	60	60	60	300

APPEARS THIS WAY
ON ORIGINAL

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Table 1b

NUMBER OF ANIMALS DIED

Species: Mouse
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	2	2	3	1	2	10
53-78	9	8	6	6	9	38
79-91	4	4	8	6	12	34
92-103	17	18	17	19	19	90
104-105	28	28	26	28	18	128
Total	60	60	60	60	60	300

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ON ORIGINAL

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Table 2a

INTERCURRENT MORTALITY RATES

Intercurrent Mortality Rates
Species: Mouse
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
Time(-wks)	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
0-52	1	60	1.7	6	60	10.0	4	60	6.7	10	60	16.7	18	60	30.0
53-78	4	59	8.3	9	54	25.0	11	56	25.0	23	50	55.0	27	42	75.0
79-81	55	60	91.7	45	60	75.0	45	60	75.0	27	60	45.0	15	60	25.0

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Table 2b

INTERCURRENT MORTALITY RATES

Species: Mouse
Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
Time(-wks)	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
0-52	2	60	3.3	2	60	3.3	3	60	5.0	1	60	1.7	2	60	3.3
53-78	9	58	18.3	8	58	16.7	6	57	15.0	6	59	11.7	9	58	18.3
79-91	4	49	25.0	4	50	23.3	8	51	28.3	6	53	21.7	12	49	38.3
92-103	17	45	53.3	18	46	53.3	17	43	56.7	19	47	53.3	19	37	70.0
104-105	28	60	46.7	28	60	46.7	26	60	43.3	28	60	46.7	18	60	30.0

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Table 3a

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	82.05	0.0000
	Depart from Trend	3.92	0.2700
	Homogeneity	85.97	0.0000
Kruskal-Wallis	Dose-Mortality Trend	77.91	0.0000
	Depart from Trend	4.08	0.2526
	Homogeneity	81.99	0.0000

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Table 3b

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	4.40	0.0360
	Depart from Trend	1.24	0.7440
	Homogeneity	5.63	0.2282
Kruskal-Wallis	Dose-Mortality Trend	3.72	0.0537
	Depart from Trend	1.45	0.6929
	Homogeneity	5.18	0.2697

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Table 4 (Part I)

Mouse: Organs and Organ Codes

1	ADRENAL(S)
2	AORTA
3	BONE MARROW
4	BRAIN
5	CECUM
6	COLON
7	DUODENUM
8	EPIDIDYMIDES
9	ESOPHAGUS
10	EXORBIT.LACR.GL.
11	EYE(S)-OPTIC.NER
12	GALL BLADDER
13	HARDERIAN GLANDS
14	HEART
15	HEMOPOIETIC SYS
16	ILEUM
17	JEJUNUM
18	KIDNEY(S)
19	LIVER
20	LUNG(S)-BRONCHI
21	LYMPH NODES
22	MAMMARY GLAND
23	MESENTERIC L.N.
24	OVARIES
25	PANCREAS
26	PARATHYROID(S)
27	PAROTID(S)
28	PERITONEAL CAV.
29	PITUITARY
30	PLEURAL CAVITY
31	PROSTATE
32	RECTUM
33	SCIATIC NERVE
34	SEMINAL VESICLES
35	SKELETAL MUSCLE
36	SKIN
37	SPINAL CORD CERV
38	SPINAL CORD LUMB
39	SPINAL CORD THOR
40	SPLEEN
41	STERNEBRA(E)
42	STOMACH
43	SUBMAXILL. L.N.
44	SUBMAXILL. S.G.
45	TAIL
46	TESTES
47	THYMUS
48	THYROID(S)
49	TONGUE
50	TRACHEA
51	URINARY BLADDER
52	UTERUS
53	VAGINA
54	ZYMBAL'S GLAND

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Table 4 (Part II)

Mouse: Tumors and Tumor Codes

1	ADRENAL(S) BENIGN TUMOR CORTICAL ADENOMA
2	ADRENAL(S) BENIGN TUMOR PHEOCHROMOCYTOMA
3	ADRENAL(S) MALIGNANT TUMOR CORTICAL ADENOCARCINOMA
4	ADRENAL(S) MALIGNANT TUMOR PHEOCHROMOCYTOMA
5	COLON MALIGNANT TUMOR ADENOCARCINOMA
6	HARDERIAN GLANDS BENIGN TUMOR HARDERIAN ADENOMA
7	HEMOPOIETIC SYS MALIGNANT TUMOR GRANULOCYTIC SARCOMA
8	HEMOPOIETIC SYS MALIGNANT TUMOR HISTIOCYTIC SARCOMA
9	HEMOPOIETIC SYS MALIGNANT TUMOR MALIGNANT LYMPHOMA
10	KIDNEY(S) BENIGN TUMOR HEMANGIOMA
11	LIVER BENIGN TUMOR CHOLANGIOMA
12	LIVER BENIGN TUMOR HEPATOCELLULAR ADENOMA
13	LIVER MALIGNANT TUMOR HEPATOCELLULAR CARCINOMA
14	LUNG(S)-BRONCHI BENIGN TUMOR PULMONARY ADENOMA
15	LUNG(S)-BRONCHI MALIGNANT TUMOR PULMONARY CARCINOMA
16	MAMMARY GLAND MALIGNANT TUMOR MAMMARY ADENOACANTHOMA
17	MAMMARY GLAND MALIGNANT TUMOR MAMMARY ADENOCARCINOMA
18	OVARIES BENIGN TUMOR CYSTADENOMA
19	OVARIES BENIGN TUMOR FALLOPIAN TUBE ADENOMA
20	OVARIES BENIGN TUMOR GRANULOSA CELL TUMOR
21	OVARIES BENIGN TUMOR GRANULOSA-THECAL TUMOR, LUTEINISED
22	OVARIES BENIGN TUMOR LEIOMYOMA
23	OVARIES BENIGN TUMOR LUTEOMA
24	OVARIES MALIGNANT TUMOR GRANULOSA CELL TUMOR
25	PITUITARY BENIGN TUMOR ADENOMA OF PARS DISTALIS
26	PLEURAL CAVITY MALIGNANT TUMOR FIBROSARCOMA
27	SKIN BENIGN TUMOR SQUAMOUS PAPILLOMA
28	SKIN MALIGNANT TUMOR FIBROLIPOSARCOMA
29	SKIN MALIGNANT TUMOR FIBROSARCOMA
30	STOMACH BENIGN TUMOR SQUAMOUS PAPILLOMA
31	SUBMAXILL. S.G. MALIGNANT TUMOR SALIVARY ADENOCARCINOMA
32	TONGUE BENIGN TUMOR SQUAMOUS PAPILLOMA
33	URINARY BLADDER BENIGN TUMOR LEIOMYOMA
34	URINARY BLADDER BENIGN TUMOR TRANSITIONAL CELL PAPILLOMA
35	UTERUS BENIGN TUMOR HEMANGIOMA
36	UTERUS BENIGN TUMOR LEIOMYOMA
37	UTERUS MALIGNANT TUMOR ENDOMETRIAL SARCOMA
38	UTERUS MALIGNANT TUMOR LEIOMYOSARCOMA
39	ZYMBAL'S GLAND MALIGNANT TUMOR ZYMBAL'S GLAND TUMOR

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0130

Table 5a

Analysis of Carcinogenic Potential in **Male Mouse**
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: November 11, 1997 (9:11)
Source: C:\TOLTERODINE\p9359m.dat

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 5 15 30)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----					EXACT PROB -PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
ADRENAL(S)	(1)	IN	79-81	1	1	1	0	0	0	1.0000	0.8260	0.8361
ADRENAL(S) BENIGN TUMOR C	(1)	IN	79-81	2	52	44	45	27	15			
Spontaneous tumor rate 2% in ctrl. - Total				-	1	1	0	0	0			
ADRENAL(S)	(1)	IN	79-81	1	1	0	0	0	0	1.0000	0.7460	0.7638
ADRENAL(S) MALIGNANT TUMO	(4)	IN	79-81	2	52	45	45	27	15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	0	0	0			
HARDERIAN GLANDS	(13)	IN	79-81	1	1	3	0	0	1	0.3702	0.3605	0.3691
HARDERIAN GLANDS BENIGN T	(6)	IN	79-81	2	54	42	45	27	14			
		FA	59	1	0	0	0	1	0			
		FA	59	2	57	51	56	45	35			
Spontaneous tumor rate 3% in ctrl. - Total				-	1	3	0	1	1			
HEMOPOIETIC SYS	(15)	IN	79-81	1	0	0	0	0	1	0.0802	0.0029	0.0035
HEMOPOIETIC SYS MALIGNANT	(7)	IN	79-81	2	55	45	45	27	14			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	0	0	1			
HEMOPOIETIC SYS	(15)	IN	79-81	1	1	0	0	0	1	0.1746	0.0685	0.0739
HEMOPOIETIC SYS MALIGNANT	(8)	IN	79-81	2	54	45	45	27	14			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	0	0	1			
HEMOPOIETIC SYS	(15)	IN	53-78	1	0	0	0	1	0	0.5569	0.5581	0.5716
HEMOPOIETIC SYS MALIGNANT	(9)	IN	53-78	2	4	9	11	22	27			
		IN	79-81	1	0	0	1	0	0			
		IN	79-81	2	55	45	44	27	15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	1	1	0			
KIDNEY(S)	(18)	IN	79-81	1	1	0	0	0	0	1.0000	0.7443	0.7623
KIDNEY(S) BENIGN TUMOR HE	(10)	IN	79-81	2	54	45	45	27	15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	0	0	0			
LIVER	(19)	IN	79-81	1	0	1	0	0	0	1.0000	0.7443	0.7623
LIVER BENIGN TUMOR CHOLAN	(11)	IN	79-81	2	55	44	45	27	15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1	0	0	0			
LIVER	(19)	IN	53-78	1	0	0	1	0	0	0.9676	0.9574	0.9583
LIVER BENIGN TUMOR HEPATO	(12)	IN	53-78	2	3	9	10	23	26			
		IN	79-81	1	10	12	11	4	0			
		IN	79-81	2	45	33	34	23	15			
		FA	75	1	0	0	0	0	1			
		FA	75	2	55	46	49	31	18			
Spontaneous tumor rate 18% in ctrl. - Total				-	10	12	12	4	1			
LIVER	(19)	IN	53-78	1	1	0	0	1	0	0.9072	0.8845	0.8879
LIVER MALIGNANT TUMOR HEP	(13)	IN	53-78	2	2	9	11	22	27			
		IN	79-81	1	1	3	2	1	0			
		IN	79-81	2	54	42	43	26	15			
Spontaneous tumor ra[redacted] 4% in ctrl. - Total				-	2	3	2	2	0			
LUNG(S)-BRONCHI	(20)	IN	53-78	1	0	1	0	0	0	0.2097	0.1969	0.1999
LUNG(S)-BRONCHI BENIGN TU	(14)	IN	53-78	2	4	8	10	21	27			
		IN	79-81	1	6	5	7	4	3			
		IN	79-81	2	49	40	38	23	12			
		FA	68	1	0	0	0	1	0			
		FA	68	2	57	49	52	34	28			
		FA	75	1	0	0	1	0	0			
		FA	75	2	55	46	48	31	19			
		FA	76	1	0	0	0	1	0			
		FA	76	2	55	46	47	30	18			
Spontaneous tumor rate 10% in ctrl. - Total				-	6	6	8	6	3			
LUNG(S)-BRONCHI	(20)	IN	79-81	1	1	0	1	0	0	0.8577	0.7999	0.8089
LUNG(S)-BRONCHI MALIGNANT	(15)	IN	79-81	2	54	45	44	27	15			
		FA	74	1	1	0	0	0	0			
		FA	74	2	55	46	50	33	19			
Spontaneous tumor rate 2% in ctrl. - Total				-	2	0	1	0	0			

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Table 5a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----					EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
SKIN	(36)	IN	79-81	1	0	0	1	0	0	0.7154	0.7015	0.7153
SKIN BENIGN TUMOR SQUAMOU	(27)	IN	79-81	2	54	45	44	27	15			
		FA	79	1	1	0	0	0	0			
		FA	79	2	54	45	45	27	15			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	1	0	1	0	0			
STOMACH	(42)	IN	79-81	1	0	0	0	0	1	0.0806	0.0030	0.0036
STOMACH BENIGN TUMOR SQUA	(30)	IN	79-81	2	55	45	44	27	14			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0	0	0	0	1			
TONGUE	(49)	FA	57	1	0	0	0	1	0	0.3306	0.2494	0.2651
TONGUE BENIGN TUMOR SQUAM	(32)	FA	57	2	57	53	56	48	33			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0	0	0	1	0			
URINARY BLADDER	(51)	IN	79-81	1	0	0	1	1	0	0.2444	0.2479	0.2608
URINARY BLADDER BENIGN TU	(33)	IN	79-81	2	55	45	44	26	15			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0	0	1	1	0			
URINARY BLADDER	(51)	FA	71	1	0	0	0	0	1	0.1095	0.0082	0.0094
URINARY BLADDER BENIGN TU	(34)	FA	71	2	56	48	50	33	22			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0	0	0	0	1			

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Table 5b

Analysis of Carcinogenic Potential in **Female Mouse**
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: November 11, 1997 (10:35)
Source: C:\TOLTERODINE\P9359F.DAT

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 5 15 30)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----					EXACT PROB	ASYMP TOTIC	ASYMP(CONTI NUITY CORR) -PR(STATISTIC.GE.OBSERVED)
ADRENAL(S)	(1)	IN	104-105	1	0	1	0	0	0	1.0000	0.7934	0.8068
ADRENAL(S) BENIGN TUMOR P	(2)	IN	104-105	2	28	27	26	28	18			
Spontaneous tumor rate LE 1% in ctrl. - Total		-		-	0	1	0	0	0			
ADRENAL(S)	(1)	IN	53-78	1	1	0	0	0	0	1.0000	0.8799	0.8860
ADRENAL(S) MALIGNANT TUMO	(3)	IN	53-78	2	8	8	6	6	9			
		IN	104-105	1	0	1	0	0	0			
		IN	104-105	2	28	27	26	28	18			
Spontaneous tumor rate 2% in ctrl. - Total		-		-	1	1	0	0	0			
HARDERIAN GLANDS	(13)	IN	92-103	1	0	2	0	0	0	0.8415	0.8254	0.8296
HARDERIAN GLANDS BENIGN T	(6)	IN	92-103	2	16	16	17	17	18			
		IN	104-105	1	1	1	0	0	0			
		IN	104-105	2	27	27	26	28	17			
		FA	86	1	0	0	0	1	0			
		FA	86	2	47	49	48	49	42			
		FA	93	1	0	0	0	1	0			
		FA	93	2	44	46	43	46	35			
		FA	94	1	1	0	0	0	0			
		FA	94	2	40	43	41	44	34			
		FA	102	1	0	0	0	1	0			
		FA	102	2	33	37	35	34	23			
Spontaneous tumor rate 4% in ctrl. - Total		-		-	2	3	0	3	0			
HEMOPOIETIC SYS	(15)	IN	53-78	1	0	0	0	1	0	0.3381	0.3150	0.3203
HEMOPOIETIC SYS MALIGNANT	(8)	IN	53-78	2	9	8	6	5	9			
		IN	92-103	1	0	0	4	3	1			
		IN	92-103	2	17	18	13	16	18			
Spontaneous tumor rate LE 1% in ctrl. - Total		-		-	0	0	4	4	1			
HEMOPOIETIC SYS	(15)	IN	53-78	1	2	1	0	0	0	0.9949	0.9920	0.9921
HEMOPOIETIC SYS MALIGNANT	(9)	IN	53-78	2	7	7	6	6	9			
		IN	79-91	1	1	1	2	1	2			
		IN	79-91	2	2	3	6	5	10			
		IN	92-103	1	3	2	2	2	1			
		IN	92-103	2	14	15	15	17	18			
		IN	104-105	1	2	1	4	1	0			
		IN	104-105	2	25	27	22	27	18			
		FA	90	1	1	0	0	0	0			
		FA	90	2	45	46	44	48	38			
		FA	93	1	0	1	0	0	0			
		FA	93	2	44	45	43	47	37			
		FA	105	1	1	0	0	0	0			
		FA	105	2	2	5	4	7	0			
Spontaneous tumor rate 13% in ctrl. - Total		-		-	10	6	8	4	3			
LIVER	(19)	IN	104-105	1	3	1	0	0	0	1.0000	0.9511	0.9535
LIVER BENIGN TUMOR HEPATO	(12)	IN	104-105	2	25	27	26	28	18			
Spontaneous tumor rate 3% in ctrl. - Total		-		-	3	1	0	0	0			
LIVER	(19)	IN	104-105	1	1	0	1	0	0	0.8105	0.7941	0.8036
LIVER MALIGNANT TUMOR HEP	(13)	IN	104-105	2	27	28	25	28	18			
Spontaneous tumor rate LE 1% in ctrl. - Total		-		-	1	0	1	0	0			
LUNG(S)-BRONCHI	(20)	IN	79-91	1	0	0	0	0	1	0.4562	0.4485	0.4519
LUNG(S)-BRONCHI BENIGN TU	(14)	IN	79-91	2	4	4	5	6	10			
		IN	92-103	1	0	1	3	1	0			
		IN	92-103	2	17	17	13	17	18			
		IN	104-105	1	4	6	2	1	2			
		IN	104-105	2	24	22	24	26	16			
		FA	69	1	0	0	0	0	1			
		FA	69	2	54	55	54	55	52			
		FA	81	1	0	0	1	0	1			
		FA	81	2	49	50	50	52	46			
		FA	84	1	0	0	1	0	0			
		FA	84	2	47	49	49	51	45			
		FA	91	1	0	0	1	0	0			
		FA	91	2	45	46	43	47	37			
		FA	94	1	0	0	0	1	0			
		FA	94	2	41	43	41	43	36			
		FA	99	1	0	0	0	0	1			

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Table 5b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP(CONTI NUITY CORR) =PR(STATISTIC.GE.OBSERVED)
		FA	99	2	35 39 38 37 30			
		FA	102	1	0 0 1 0 0			
		FA	102	2	33 37 34 35 24			
		FA	104	1	0 0 0 1 0			
		FA	104	2	28 28 26 27 18			
Spontaneous tumor rate 9% in ctrl.		- Total		-	4 7 9 4 6			
LUNG(S)-BRONCHI	(20)	IN	53-78	1	0 0 0 1 0	0.9287	0.9171	0.9187
LUNG(S)-BRONCHI MALIGNANT	(15)	IN	53-78	2	9 8 6 5 9			
		IN	79-91	1	0 1 1 0 0			
		IN	79-91	2	4 3 7 6 12			
		IN	92-103	1	2 2 1 1 2			
		IN	92-103	2	15 16 16 18 17			
		IN	104-105	1	4 1 1 1 0			
		IN	104-105	2	24 27 24 27 18			
		FA	104	1	0 0 1 0 0			
		FA	104	2	28 28 25 28 18			
Spontaneous tumor rate 8% in ctrl.		- Total		-	6 4 4 3 2			
MAMMARY GLAND	(22)	IN	79-91	1	0 0 1 0 0	0.5810	0.5861	0.5975
MAMMARY GLAND MALIGNANT T	(16)	IN	79-91	2	4 4 7 5 10			
		IN	92-103	1	0 0 0 1 0			
		IN	92-103	2	17 17 17 17 18			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	0 0 1 1 0			
MAMMARY GLAND	(22)	IN	53-78	1	0 0 1 0 1	0.9345	0.9217	0.9233
MAMMARY GLAND MALIGNANT T	(17)	IN	53-78	2	8 7 5 6 8			
		IN	79-91	1	1 0 0 0 0			
		IN	79-91	2	3 4 8 5 10			
		IN	92-103	1	1 2 2 0 0			
		IN	92-103	2	16 15 15 18 18			
		IN	104-105	1	2 2 2 3 0			
		IN	104-105	2	26 26 24 25 18			
Spontaneous tumor rate 7% in ctrl.		- Total		-	4 4 5 3 1			
OVARIES	(24)	FA	102	1	0 0 1 0 0	0.5732	0.6363	0.6541
OVARIES BENIGN TUMOR CYST	(18)	FA	102	2	33 37 34 35 24			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	0 0 1 0 0			
OVARIES	(24)	IN	92-103	1	1 0 0 0 0	1.0000	0.8177	0.8289
OVARIES BENIGN TUMOR FALL	(19)	IN	92-103	2	16 18 16 19 19			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	1 0 0 0 0			
OVARIES	(24)	IN	104-105	1	0 0 0 1 0	0.3594	0.2667	0.2827
OVARIES BENIGN TUMOR GRAN	(20)	IN	104-105	2	28 28 26 27 18			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	0 0 0 1 0			
OVARIES	(24)	IN	104-105	1	0 1 0 0 0	1.0000	0.7934	0.8068
OVARIES BENIGN TUMOR GRAN	(21)	IN	104-105	2	28 27 26 28 18			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	0 1 0 0 0			
OVARIES	(24)	IN	92-103	1	0 0 0 1 0	0.6623	0.6281	0.6367
OVARIES BENIGN TUMOR LEIO	(22)	IN	92-103	2	17 17 16 17 19			
		FA	95	1	0 0 0 1 0			
		FA	95	2	40 42 40 40 35			
		FA	103	1	0 1 0 0 0			
		FA	103	2	33 33 32 32 23			
		FA	104	1	0 1 0 0 0			
		FA	104	2	28 27 26 28 18			
Spontaneous tumor rate 2% in ctrl.		- Total		-	0 2 0 2 0			
OVARIES	(24)	FA	71	1	0 0 1 0 0	0.5933	0.6652	0.6811
OVARIES BENIGN TUMOR LUTE	(23)	FA	71	2	54 55 52 54 52			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	0 0 1 0 0			
OVARIES	(24)	FA	97	1	1 0 0 0 0	0.3459	0.2204	0.2301
OVARIES MALIGNANT TUMOR G	(24)	FA	97	2	37 41 38 39 34			
		FA	101	1	0 0 0 0 1			
		FA	101	2	33 38 35 35 24			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	1 0 0 0 1			
PITUITARY	(29)	IN	104-105	1	0 1 0 0 0	0.8282	0.8042	0.8132
PITUITARY BENIGN TUMOR AD	(25)	IN	104-105	2	26 25 26 28 18			
		FA	100	1	0 0 1 0 0			
		FA	100	2	31 37 36 34 27			
Spontaneous tumor rate LE 1% in ctrl.		- Total		-	0 1 1 0 0			

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Table 5b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
PLEURAL CAVITY	(30)	IN	92-103	1	0 0 1 0 0	0.6111	0.6815	0.6968
PLEURAL CAVITY MALIGNANT	(26)	IN	92-103	2	17 18 16 19 19			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 1 0 0			
SKIN	(36)	IN	53-78	1	0 0 0 0 1	0.2432	0.0551	0.0598
SKIN MALIGNANT TUMOR FIBR	(28)	IN	53-78	2	9 7 6 6 8			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 0 1			
SKIN	(36)	IN	92-103	1	0 1 0 0 0	1.0000	0.9317	0.9351
SKIN MALIGNANT TUMOR FIBR	(29)	IN	92-103	2	16 16 17 17 19			
		IN	104-105	1	0 1 0 0 0			
		IN	104-105	2	28 27 26 28 18			
		FA	95	1	1 0 0 0 0			
		FA	95	2	39 41 41 40 35			
Spontaneous tumor rate 3% in ctrl. - Total				-	1 2 0 0 0			
SUBMAXILL. S.G.	(44)	IN	92-103	1	1 0 0 0 0	1.0000	0.8198	0.8309
SUBMAXILL. S.G. MALIGNANT	(31)	IN	92-103	2	16 17 17 19 19			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1 0 0 0 0			
UTERUS	(52)	IN	0-52	1	0 1 0 0 0	0.9242	0.8716	0.8772
UTERUS BENIGN TUMOR HEMAN	(35)	IN	0-52	2	2 1 3 1 2			
		IN	104-105	1	0 1 1 0 0			
		IN	104-105	2	28 27 25 28 18			
Spontaneous tumor rate 2% in ctrl. - Total				-	0 2 1 0 0			
UTERUS	(52)	IN	104-105	1	1 1 2 1 0	0.8348	0.8194	0.8232
UTERUS BENIGN TUMOR LEIOM	(36)	IN	104-105	2	27 27 23 27 18			
		FA	77	1	1 0 0 0 0			
		FA	77	2	52 52 52 54 49			
		FA	98	1	1 0 0 0 0			
		FA	98	2	35 41 38 38 32			
		FA	99	1	0 0 0 0 1			
		FA	99	2	35 39 38 37 30			
		FA	102	1	0 1 1 0 0			
		FA	102	2	33 36 34 35 24			
		FA	104	1	0 0 1 0 0			
		FA	104	2	28 28 25 28 18			
Spontaneous tumor rate 4% in ctrl. - Total				-	3 2 4 1 1			
UTERUS	(52)	IN	92-103	1	1 1 0 0 0	1.0000	0.9605	0.9624
UTERUS MALIGNANT TUMOR EN	(37)	IN	92-103	2	16 17 17 19 19			
		IN	104-105	1	1 0 0 0 0			
		IN	104-105	2	27 28 26 28 18			
		FA	76	1	0 1 0 0 0			
		FA	76	2	53 53 52 55 50			
Spontaneous tumor rate 3% in ctrl. - Total				-	2 2 0 0 0			
UTERUS	(52)	IN	104-105	1	1 0 1 1 0	0.6143	0.6218	0.6323
UTERUS MALIGNANT TUMOR LE	(38)	IN	104-105	2	27 28 25 27 18			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1 0 1 1 0			
ZYMBAL'S GLAND	(54)	FA	69	1	0 0 0 0 1	0.1956	0.0382	0.0420
ZYMBAL'S GLAND MALIGNANT	(39)	FA	69	2	54 55 54 55 52			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 0 1			
COLON	(6)	IN	79-91	1	0 0 0 0 1	0.3636	0.1088	0.1164
COLON MALIGNANT TUMOR ADE	(5)	IN	79-91	2	4 4 8 5 11			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 0 1			

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Table 6a

NUMBER OF ANIMALS DIED

Species: Rat
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time interval						
0-52	2	1	1	1	.	5
53-78	4	5	7	6	7	29
79-91	6	3	8	6	1	24
92-102	8	11	8	4	12	43
103-105	40	40	36	43	40	199
Total	60	60	60	60	60	300

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Table 6b

NUMBER OF ANIMALS DIED

Species: Rat
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	4	.	2	.	3	9
53-78	9	11	11	11	7	49
79-91	9	6	11	9	4	39
92-102	9	9	10	15	12	55
103-105	29	34	26	25	34	148
Total	60	60	60	60	60	300

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Table 7a

INTERCURRENT MORTALITY RATES

Species: Rat
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
Time(-wks)															
0-52	2	60	3.3	1	60	1.7	1	60	1.7	1	60	1.7	.	.	.
53-78	4	58	10.0	5	59	10.0	7	59	13.3	6	59	11.7	7	60	11.7
79-91	6	54	20.0	3	54	15.0	8	52	26.7	6	53	21.7	1	53	13.3
92-102	8	48	33.3	11	51	33.3	8	44	40.0	4	47	28.3	12	52	33.3
103-105	40	60	66.7	40	60	66.7	36	60	60.0	43	60	71.7	40	60	66.7

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Table 7b

INTERCURRENT MORTALITY RATES

Species: Rat
Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
Time(-wks)															
0-52	4	60	6.7	.	.	.	2	60	3.3	.	.	.	3	60	5.0
53-78	9	56	21.7	11	60	18.3	11	58	21.7	11	60	18.3	7	57	16.7
79-91	9	47	36.7	6	49	28.3	11	47	40.0	9	49	33.3	4	50	23.3
92-102	9	38	51.7	9	43	43.3	10	36	56.7	15	40	58.3	12	46	43.3
103-105	29	60	48.3	34	60	56.7	26	60	43.3	25	60	41.7	34	60	56.7

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Table 8a

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.19	0.6627
	Depart from Trend	1.74	0.6272
	Homogeneity	1.93	0.7479
Kruskal-Wallis	Dose-Mortality Trend	0.23	0.6281
	Depart from Trend	1.72	0.6331
	Homogeneity	1.95	0.7446

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Table 8b

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.26	0.6076
	Depart from Trend	3.82	0.2816
	Homogeneity	4.08	0.3949
Kruskal-Wallis	Dose-Mortality Trend	0.41	0.5219
	Depart from Trend	2.92	0.4044
	Homogeneity	3.33	0.5045

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Table 9 (Part I)

Rat: Organs and Organ Codes

1	ADRENAL(S)
2	AORTA
3	BONE
4	BONE MARROW
5	BRAIN
6	CECUM
7	COLON
8	DUODENUM
9	EAR(S)
10	EPIDIDYMIDES
11	ESOPHAGUS
12	EXORBIT.LACR.GL.
13	EYE(S)-OPTIC.NER
14	HARDERIAN GLANDS
15	HEART
16	HEMOPOIETIC SYST
17	ILEUM
18	JEJUNUM
19	KIDNEY(S)
20	LIVER
21	LUNG(S)-BRONCHI
22	LYMPH NODES
23	MAMMARY GLAND
24	MESENTERIC L.N.
25	MESENTERY
26	OVARIES
27	PANCREAS
28	PARATHYROID(S)
29	PAROTID(S)
30	PAWS/FEET
31	PERITONEAL CAV.
32	PITUITARY
33	PLEURAL CAVITY
34	PROSTATE
35	RECTUM
36	SCIATIC NERVE
37	SEMINAL VESICLES
38	SKELETAL MUSCLE
39	SKIN
40	SPINAL CORD CERV
41	SPINAL CORD LUMB
42	SPINAL CORD THOR
43	SPLEEN
44	STERNEBRA(E)
45	STOMACH
46	SUBMAXILL. L.N.
47	SUBMAXILL. S.G.
48	TESTES
49	THYMUS
50	THYROID(S)
51	TONGUE
52	TRACHEA
53	URINARY BLADDER
54	UTERUS
55	VAGINA

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Table 9 (Part II)

Rat: Tumors and Tumor Codes

1 ADRENAL(S) BENIGN TUMOR CORTICAL ADENOMA
2 ADRENAL(S) BENIGN TUMOR PHEOCHROMOCYTOMA
3 ADRENAL(S) MALIGNANT TUMOR CORTICAL ADENOCARCINOMA
4 ADRENAL(S) MALIGNANT TUMOR PHEOCHROMOCYTOMA
5 BONE MALIGNANT TUMOR CHONDROSARCOMA
6 BONE MALIGNANT TUMOR OSTEOSARCOMA
7 BRAIN BENIGN TUMOR GRANULAR CELL TUMOR
8 BRAIN MALIGNANT TUMOR ASTROCYTOMA
9 BRAIN MALIGNANT TUMOR OLIGODENDROGLIOMA
10 CECUM MALIGNANT TUMOR SCHWANNOMA
11 DUODENUM MALIGNANT TUMOR ADENOCARCINOMA
12 HEART MALIGNANT TUMOR ATRIOCAVAL MESOTHELIOMA
13 HEART MALIGNANT TUMOR ENDOCARDIAL SCHWANNOMA
14 HEMOPOIETIC SYST MALIGNANT TUMOR GRANULOCYTIC LEUKEMIA
15 HEMOPOIETIC SYST MALIGNANT TUMOR HISTIOCYTIC SARCOMA
16 HEMOPOIETIC SYST MALIGNANT TUMOR LARGE GRANULAR LYMPHOCYTE LEUKEMIA
17 HEMOPOIETIC SYST MALIGNANT TUMOR LYMPHOMA
18 ILEUM BENIGN TUMOR LEIOMYOMA
19 KIDNEY(S) BENIGN TUMOR RENAL LIPOMA
20 KIDNEY(S) MALIGNANT TUMOR CARCINOMA
21 KIDNEY(S) MALIGNANT TUMOR RENAL LIPOSARCOMA
22 LIVER BENIGN TUMOR HEPATOCELLULAR ADENOMA
23 LIVER MALIGNANT TUMOR HEMANGIOSARCOMA
24 LIVER MALIGNANT TUMOR HEPATOCELLULAR ADENOCARCINOMA
25 LUNG(S)-BRONCHI BENIGN TUMOR BRONCHIOLO-ALVEOLAR ADENOMA
26 LYMPH NODES MALIGNANT TUMOR HEMANGIOSARCOMA
27 MAMMARY GLAND BENIGN TUMOR ADENOMA
28 MAMMARY GLAND BENIGN TUMOR FIBROADENOMA
29 MAMMARY GLAND BENIGN TUMOR LIPOMA
30 MAMMARY GLAND BENIGN TUMOR SCHWANNOMA
31 MAMMARY GLAND MALIGNANT TUMOR ADENOCARCINOMA
32 MESENTERIC L.N. MALIGNANT TUMOR HEMANGIOSARCOMA
33 OVARIES BENIGN TUMOR GRANULOSA CELL TUMOR
34 OVARIES BENIGN TUMOR MIXED SEX CORD STROMAL TUMOR
35 OVARIES MALIGNANT TUMOR THECOMA
36 PANCREAS BENIGN TUMOR ISLET CELL ADENOMA
37 PANCREAS BENIGN TUMOR MIXED TUMOR
38 PANCREAS MALIGNANT TUMOR ISLET CELL ADENOCARCINOMA
39 PARATHYROID(S) BENIGN TUMOR ADENOMA
40 PERITONEAL CAV. MALIGNANT TUMOR INTESTINAL ADENOCARCINOMA
41 PERITONEAL CAV. MALIGNANT TUMOR SCHWANNOMA
42 PITUITARY BENIGN TUMOR ADENOMA OF PARS DISTALIS
43 PITUITARY MALIGNANT TUMOR ADENOCARCINOMA OF PARS DISTALIS
44 PLEURAL CAVITY BENIGN TUMOR HIBERNOMA
45 PROSTATE BENIGN TUMOR ADENOMA
46 RECTUM BENIGN TUMOR ADENOMA
47 RECTUM BENIGN TUMOR FIBROMA
48 SEMINAL VESICLES MALIGNANT TUMOR ADENOCARCINOMA
49 SKELETAL MUSCLE MALIGNANT TUMOR RHABDOMYOSARCOMA
50 SKIN BENIGN TUMOR BASAL CELL TUMOR
51 SKIN BENIGN TUMOR FIBROMA
52 SKIN BENIGN TUMOR FIBROUS HISTIOCYTOMA
53 SKIN BENIGN TUMOR HAIR FOLLICLE TUMOR
54 SKIN BENIGN TUMOR KERATOACANTHOMA
55 SKIN BENIGN TUMOR LIPOMA
56 SKIN BENIGN TUMOR SEBACEOUS ADENOMA
57 SKIN BENIGN TUMOR SQUAMOUS CELL PAPILLOMA
58 SKIN MALIGNANT TUMOR FIBROSARCOMA
59 SKIN MALIGNANT TUMOR FIBROUS HISTIOCYTOMA
60 SKIN MALIGNANT TUMOR HEMANGIOSARCOMA
61 SKIN MALIGNANT TUMOR SCHWANNOMA
62 SKIN MALIGNANT TUMOR SQUAMOUS CELL CARCINOMA
63 SKIN MALIGNANT TUMOR UNDIFFERENTIATED SARCOMA
64 SPLEEN BENIGN TUMOR HEMANGIOMA
65 SPLEEN MALIGNANT TUMOR UNDIFFERENTIATED SARCOMA
66 STOMACH BENIGN TUMOR SQUAMOUS CELL PAPILLOMA
67 TESTES BENIGN TUMOR LEYDIG CELL ADENOMA
68 THYMUS MALIGNANT TUMOR THYMOMA
69 THYROID(S) BENIGN TUMOR C-CELL ADENOMA

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Table 9 (Part II)
(Continued)
Rat: Tumors and Tumor Codes

70	THYROID(S) BENIGN TUMOR FOLLICULAR ADENOMA
71	THYROID(S) MALIGNANT TUMOR C-CELL CARCINOMA
72	THYROID(S) MALIGNANT TUMOR FOLLICULAR CELL ADENOCARCINOMA
73	UTERUS BENIGN TUMOR FIBROMA
74	UTERUS BENIGN TUMOR GRANULAR CELL TUMOR
75	UTERUS MALIGNANT TUMOR LEIOMYOSARCOMA
76	UTERUS MALIGNANT TUMOR SCHWANNOMA
77	UTERUS MALIGNANT TUMOR SQUAMOUS CELL CARCINOMA
78	VAGINA BENIGN TUMOR FIBROMA

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Table 10a

Analysis of Carcinogenic Potential in **Male Rat**
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: November 7, 1997 (11:16)
Source: C:\TOLTERODINE\p9350m.dat

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 5 15 30)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
ADRENAL(S)	(1)	FA 97	1	0 2 0 0 0	1.0000	0.9649	0.9666
ADRENAL(S) BENIGN TUMOR C	(1)	FA 97	2	46 46 42 47 47			
		FA 104	1	1 0 0 0 0			
		FA 104	2	34 34 30 38 35			
		FA 105	1	0 1 0 0 0			
		FA 105	2	12 13 8 17 15			
Spontaneous tumor rate 3% in ctrl. - Total			-	1 3 0 0 0			
ADRENAL(S)	(1)	FA 91	1	0 0 1 0 0	0.9800	0.9723	0.9729
ADRENAL(S) BENIGN TUMOR P	(2)	FA 91	2	49 50 44 48 52			
		FA 95	1	0 0 1 0 0			
		FA 95	2	47 49 43 47 50			
		FA 97	1	0 1 0 0 0			
		FA 97	2	46 47 42 47 47			
		FA 98	1	0 0 0 0 1			
		FA 98	2	46 46 42 47 46			
		FA 100	1	0 0 1 0 0			
		FA 100	2	43 45 39 47 45			
		FA 102	1	0 0 0 1 0			
		FA 102	2	41 42 37 43 43			
		FA 103	1	0 1 0 0 0			
		FA 103	2	40 39 36 43 40			
		FA 104	1	1 2 0 0 0			
		FA 104	2	34 32 30 38 35			
		FA 105	1	2 4 1 1 1			
		FA 105	2	10 10 7 16 14			
Spontaneous tumor rate 9% in ctrl. - Total			-	3 8 4 2 2			
ADRENAL(S)	(1)	FA 95	1	0 0 1 0 0	0.5949	0.6741	0.6895
ADRENAL(S) MALIGNANT TUMO	(4)	FA 95	2	47 49 43 47 50			
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 0 1 0 0			
HEART	(15)	IN 79-91	1	0 0 0 1 0	0.2917	0.1362	0.1511
HEART MALIGNANT TUMOR ATR	(12)	IN 79-91	2	6 3 8 5 1			
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 0 0 1 0			
HEART	(15)	IN 53-78	1	0 1 0 0 0	1.0000	0.8387	0.8490
HEART MALIGNANT TUMOR END	(13)	IN 53-78	2	4 4 7 6 7			
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 1 0 0 0			
HEMOPOIETIC SYST	(16)	IN 53-78	1	0 0 0 1 0	0.6490	0.6339	0.6408
HEMOPOIETIC SYST MALIGNAN	(15)	IN 53-78	2	4 5 7 5 7			
		IN 79-91	1	0 0 0 1 0			
		IN 79-91	2	6 3 8 5 1			
		IN 92-102	1	0 1 0 0 0			
		IN 92-102	2	8 10 8 3 12			
		IN 103-105	1	0 1 1 0 0			
		IN 103-105	2	40 39 35 43 40			
		FA 101	1	0 0 0 1 0			
		FA 101	2	43 43 37 45 43			
Spontaneous tumor rate 2% in ctrl. - Total			-	0 2 1 3 0			
HEMOPOIETIC SYST	(16)	IN 53-78	1	0 0 0 0 1	0.1801	0.1027	0.1071
HEMOPOIETIC SYST MALIGNAN	(16)	IN 53-78	2	4 5 7 6 6			
		IN 92-102	1	0 0 0 0 1			
		IN 92-102	2	8 11 8 4 11			
		FA 105	1	0 1 0 0 0			
		FA 105	2	12 13 8 17 15			
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 1 0 0 2			
HEMOPOIETIC SYST	(16)	IN 0-52	1	0 1 0 0 0	0.7321	0.7108	0.7179
HEMOPOIETIC SYST MALIGNAN	(17)	IN 0-52	2	2 0 1 1 0			
		IN 53-78	1	0 0 0 1 0			
		IN 53-78	2	4 5 7 5 7			
		FA 103	1	0 0 1 0 0			
		FA 103	2	40 40 35 43 40			
		FA 105	1	0 1 0 1 0			
		FA 105	2	12 13 8 16 15			
Spontaneous tumor rate 2% in ctrl. - Total			-	0 2 1 2 0			

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Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
KIDNEY(S)	(19)	FA	105	1	0 1 0 0 0	1.0000	0.8316	0.8421
KIDNEY(S) BENIGN TUMOR RE	(19)	FA	105	2	12 13 8 17 15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 0 0 0			
KIDNEY(S)	(19)	FA	104	1	0 0 1 1 2	0.0185	0.0122	0.0129
KIDNEY(S) MALIGNANT TUMOR	(21)	FA	104	2	35 34 29 37 33			
		FA	105	1	0 0 0 0 1			
		FA	105	2	12 14 8 17 14			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 1 1 3	(P<0.025)		
LIVER	(20)	FA	100	1	0 0 1 0 0	0.7716	0.7713	0.7778
LIVER BENIGN TUMOR HEPATO	(22)	FA	100	2	43 45 39 47 45			
		FA	104	1	1 0 1 0 0			
		FA	104	2	34 34 29 38 35			
		FA	105	1	0 0 0 1 0			
		FA	105	2	12 14 8 16 15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1 0 2 1 0			
LIVER	(20)	FA	104	1	0 1 0 0 0	1.0000	0.8154	0.8268
LIVER MALIGNANT TUMOR HEM	(23)	FA	104	2	35 33 30 38 35			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 0 0 0			
LIVER	(20)	FA	92	1	0 1 0 0 0	0.4175	0.2819	0.2923
LIVER MALIGNANT TUMOR HEP	(24)	FA	92	2	48 50 44 47 52			
		FA	104	1	0 0 0 0 1			
		FA	104	2	35 34 30 38 34			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 0 0 1			
LUNG(S)-BRONCHI	(21)	FA	82	1	0 0 0 1 0	0.4904	0.4485	0.4571
LUNG(S)-BRONCHI BENIGN TU	(25)	FA	82	2	51 53 50 51 53			
		FA	102	1	0 1 0 0 0			
		FA	102	2	41 41 37 44 43			
		FA	104	1	0 0 0 1 0			
		FA	104	2	35 34 30 37 35			
		FA	105	1	0 0 0 1 0			
		FA	105	2	12 14 8 16 15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 0 3 0			
LYMPH NODES	(22)	FA	105	1	0 0 0 0 1	0.2273	0.0557	0.0606
LYMPH NODES MALIGNANT TUM	(26)	FA	105	2	12 14 8 17 14			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 0 1			
MAMMARY GLAND	(23)	IN	103-105	1	0 0 0 1 0	0.4171	0.3364	0.3525
MAMMARY GLAND BENIGN TUMO	(28)	IN	103-105	2	40 40 36 42 40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 1 0			
MAMMARY GLAND	(23)	IN	103-105	1	0 2 0 0 3	0.1862	0.1518	0.1560
MAMMARY GLAND MALIGNANT T	(31)	IN	103-105	2	39 38 36 43 37			
		FA	104	1	1 0 0 0 0			
		FA	104	2	34 34 30 38 35			
Spontaneous tumor rate 3% in ctrl. - Total				-	1 2 0 0 3			
MESENTERIC L.N.	(24)	FA	105	1	1 0 0 0 0	1.0000	0.8316	0.8421
MESENTERIC L.N. MALIGNANT	(32)	FA	105	2	11 14 8 17 15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1 0 0 0 0			
PANCREAS	(27)	FA	95	1	0 0 1 0 0	0.5776	0.5677	0.5725
PANCREAS BENIGN TUMOR ISL	(36)	FA	95	2	47 50 43 47 50			
		FA	96	1	1 0 0 0 0			
		FA	96	2	46 50 43 47 47			
		FA	98	1	1 0 0 0 0			
		FA	98	2	45 46 42 47 47			
		FA	102	1	0 0 1 0 1			
		FA	102	2	41 42 36 44 42			
		FA	103	1	1 0 0 0 1			
		FA	103	2	39 40 36 43 39			
		FA	104	1	1 0 0 0 1			
		FA	104	2	34 34 30 38 34			
		FA	105	1	1 2 0 0 1			
		FA	105	2	11 12 8 17 14			
Spontaneous tumor rate 6% in ctrl. - Total				-	5 2 2 0 4			
PANCREAS	(27)	FA	104	1	1 0 0 0 0	1.0000	0.8154	0.8268
PANCREAS BENIGN TUMOR MIX	(37)	FA	104	2	34 34 30 38 35			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1 0 0 0 0			
PANCREAS	(27)	FA	105	1	0 1 0 0 0	1.0000	0.8316	0.8421
PANCREAS MALIGNANT TUMOR	(38)	FA	105	2	12 13 8 17 15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 0 0 0			

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Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB -PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
PARATHYROID(S)	(28)	FA	104	1	1 0 0 0 0	0.1830	0.1072	0.1120
PARATHYROID(S) BENIGN TUM	(39)	FA	104	2	23 30 30 38 31			
		FA	105	1	0 0 0 0 2			
		FA	105	2	6 13 8 17 12			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	1 0 0 0 2			
BONE	(3)	IN	53-78	1	0 1 0 0 0	1.0000	0.8387	0.8490
BONE MALIGNANT TUMOR OSTE	(6)	IN	53-78	2	4 4 7 6 7			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 1 0 0 0			
PERITONEAL CAV.	(31)	IN	79-91	1	1 0 0 0 0	1.0000	0.8101	0.8274
PERITONEAL CAV. MALIGNANT	(41)	IN	79-91	2	5 3 8 6 1			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	1 0 0 0 0			
PITUITARY	(32)	IN	53-78	1	0 2 4 1 0	0.9935	0.9924	0.9925
PITUITARY BENIGN TUMOR AD	(42)	IN	53-78	2	4 2 1 5 6			
		IN	79-91	1	4 2 5 0 0			
		IN	79-91	2	0 0 3 2 1			
		IN	92-102	1	2 6 4 2 1			
		IN	92-102	2	5 2 2 2 7			
		IN	103-105	1	1 0 0 1 0			
		IN	103-105	2	13 19 19 20 22			
		FA	61	1	0 0 1 0 0			
		FA	61	2	54 58 57 59 59			
		FA	69	1	0 0 1 0 0			
		FA	69	2	54 57 52 57 57			
		FA	70	1	0 0 0 0 1			
		FA	70	2	54 57 52 55 55			
		FA	72	1	0 1 0 0 0			
		FA	72	2	54 56 52 55 55			
		FA	80	1	1 0 0 0 0			
		FA	80	2	51 54 50 53 53			
		FA	81	1	0 0 0 1 0			
		FA	81	2	51 54 50 52 53			
		FA	83	1	0 1 0 0 0			
		FA	83	2	51 52 49 51 53			
		FA	84	1	0 0 0 1 0			
		FA	84	2	50 51 49 50 52			
		FA	90	1	0 0 0 1 0			
		FA	90	2	49 51 45 48 52			
		FA	91	1	1 0 0 1 0			
		FA	91	2	48 51 44 47 52			
		FA	93	1	0 0 0 0 1			
		FA	93	2	48 50 43 47 51			
		FA	96	1	1 1 0 0 0			
		FA	96	2	46 49 42 47 47			
		FA	97	1	0 1 0 0 0			
		FA	97	2	46 48 41 47 47			
		FA	100	1	0 1 1 0 1			
		FA	100	2	43 44 38 47 44			
		FA	102	1	0 0 0 0 2			
		FA	102	2	41 42 37 44 41			
		FA	103	1	5 1 2 2 3			
		FA	103	2	35 39 34 41 37			
		FA	104	1	12 15 9 12 11			
		FA	104	2	23 19 21 26 24			
		FA	105	1	9 5 6 8 4			
		FA	105	2	3 9 2 9 11			
Spontaneous tumor rate 60% in ctrl.		-	Total	-	36 36 33 30 24			
PROSTATE	(34)	FA	104	1	0 1 0 0 0	1.0000	0.8156	0.8270
PROSTATE BENIGN TUMOR ADE	(45)	FA	104	2	35 33 29 38 35			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 1 0 0 0			
SEMINAL VESICLES	(37)	FA	99	1	0 0 0 0 1	0.2063	0.0431	0.0472
SEMINAL VESICLES MALIGNAN	(48)	FA	99	2	44 45 41 47 45			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 0 0 0 1			
SKIN	(39)	IN	92-102	1	0 1 0 0 0	0.8224	0.8232	0.8307
SKIN BENIGN TUMOR FIBROMA	(51)	IN	92-102	2	8 10 8 4 12			
		IN	103-105	1	0 0 1 0 0			
		IN	103-105	2	40 40 35 43 40			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 1 1 0 0			
SKIN	(39)	IN	103-105	1	1 0 0 1 1	0.2952	0.2311	0.2389
SKIN BENIGN TUMOR FIBROUS	(52)	IN	103-105	2	39 40 36 42 39			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	1 0 0 1 1			

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Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----					EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
SKIN	(39)	IN	103-105	1	1	0	0	2	0	0.5824	0.5107	0.5208
SKIN BENIGN TUMOR HAIR FO	(53)	IN	103-105	2	39	40	36	41	40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	0	2	0			
SKIN	(39)	IN	103-105	1	0	1	0	0	0	1.0000	0.8135	0.8250
SKIN BENIGN TUMOR KERATOA	(54)	IN	103-105	2	40	39	36	43	40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1	0	0	0			
SKIN	(39)	IN	103-105	1	1	0	1	1	0	0.6990	0.7036	0.7123
SKIN BENIGN TUMOR LIPOMA	(55)	IN	103-105	2	39	40	35	42	40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	1	1	0			
SKIN	(39)	IN	103-105	1	0	1	0	0	1	0.4083	0.2747	0.2851
SKIN BENIGN TUMOR SEBACEO	(56)	IN	103-105	2	40	39	36	43	39			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1	0	0	1			
SKIN	(39)	IN	103-105	1	0	0	0	1	0	0.4171	0.3364	0.3525
SKIN BENIGN TUMOR SQUAMOU	(57)	IN	103-105	2	40	40	36	42	40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	0	1	0			
SKIN	(39)	IN	53-78	1	2	0	0	0	0	1.0000	0.9533	0.9557
SKIN MALIGNANT TUMOR FIBR	(58)	IN	53-78	2	2	5	7	6	7			
		IN	103-105	1	0	1	0	0	0			
		IN	103-105	2	40	39	36	43	40			
Spontaneous tumor rate 3% in ctrl. - Total				-	2	1	0	0	0			
SKIN	(39)	IN	103-105	1	0	0	0	1	0	0.4171	0.3364	0.3525
SKIN MALIGNANT TUMOR FIBR	(59)	IN	103-105	2	40	40	36	42	40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	0	1	0			
SKIN	(39)	IN	53-78	1	1	0	0	0	0	1.0000	0.8387	0.8490
SKIN MALIGNANT TUMOR HEMA	(60)	IN	53-78	2	3	5	7	6	7			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	0	0	0			
SKIN	(39)	IN	92-102	1	0	0	1	0	0	0.5581	0.6726	0.6867
SKIN MALIGNANT TUMOR SCHW	(61)	IN	92-102	2	8	11	7	4	12			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	1	0	0			
SKIN	(39)	IN	53-78	1	0	0	0	0	1	0.2344	0.2083	0.2172
SKIN MALIGNANT TUMOR SQUA	(62)	IN	53-78	2	4	5	7	6	6			
		IN	103-105	1	0	0	1	0	0			
		IN	103-105	2	40	40	35	43	40			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	1	0	1			
SKIN	(39)	IN	53-78	1	0	1	1	0	1	0.6591	0.6409	0.6493
SKIN MALIGNANT TUMOR UNDI	(63)	IN	53-78	2	4	4	6	6	6			
		IN	79-91	1	0	1	1	0	0			
		IN	79-91	2	6	2	7	6	1			
Spontaneous tumor rate 2% in ctrl. - Total				-	0	2	2	0	1			
SPLEEN	(43)	FA	105	1	0	0	0	1	0	0.4848	0.3761	0.3923
SPLEEN MALIGNANT TUMOR UN	(65)	FA	105	2	12	14	8	16	15			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	0	0	1	0			
TESTES	(48)	IN	103-105	1	0	0	0	1	0	0.2491	0.2340	0.2377
TESTES BENIGN TUMOR LEYDI	(67)	IN	103-105	2	36	39	34	40	37			
		FA	72	1	0	0	0	0	1			
		FA	72	2	54	57	53	55	54			
		FA	103	1	0	1	1	1	0			
		FA	103	2	40	39	35	42	40			
		FA	104	1	3	0	1	1	3			
		FA	104	2	32	34	29	37	32			
		FA	105	1	1	0	0	0	0			
		FA	105	2	11	14	8	17	15			
Spontaneous tumor rate 4% in ctrl. - Total				-	4	1	2	3	4			
THYMUS	(49)	IN	92-102	1	1	0	0	0	0	1.0000	0.7995	0.8103
THYMUS MALIGNANT TUMOR TH	(68)	IN	92-102	2	7	11	8	4	12			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	0	0	0			
BRAIN	(5)	FA	103	1	0	1	0	0	1	0.4083	0.2747	0.2851
BRAIN BENIGN TUMOR GRANUL	(7)	FA	103	2	40	39	36	43	39			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1	0	0	1			
BRAIN	(5)	IN	0-52	1	0	0	0	1	0	0.2681	0.2438	0.2512
BRAIN MALIGNANT TUMOR AST	(8)	IN	0-52	2	2	1	1	0	0			
		IN	92-102	1	0	1	0	0	0			
		IN	92-102	2	8	10	8	4	12			
		FA	88	1	0	0	1	0	0			
		FA	88	2	50	51	48	49	52			

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Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP(CONTI NUITY CORR) =PR(STATISTIC.GE.OBSERVED)
			FA 104	1	0 0 0 0 1			
			FA 104	2	35 34 30 38 34			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 1 1 1 1			
BRAIN	(5)	IN	0-52	1	1 0 0 0 0	0.4977	0.4914	0.5056
BRAIN MALIGNANT TUMOR OLI	(9)	IN	0-52	2	1 1 1 1 0			
		IN	92-102	1	0 0 0 1 0			
		IN	92-102	2	8 11 8 3 12			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	1 0 0 1 0			
THYROID(S)	(50)	FA	93	1	0 0 0 0 1	0.5154	0.5063	0.5101
THYROID(S) BENIGN TUMOR C	(69)	FA	93	2	48 50 44 47 51			
		FA	96	1	0 1 0 0 0			
		FA	96	2	47 49 43 47 47			
		FA	100	1	0 0 1 0 0			
		FA	100	2	43 45 39 47 45			
		FA	102	1	0 2 0 0 0			
		FA	102	2	41 40 37 44 43			
		FA	103	1	0 2 0 0 0			
		FA	103	2	40 38 36 43 40			
		FA	104	1	2 4 0 1 3			
		FA	104	2	33 30 30 37 32			
		FA	105	1	2 0 0 0 3			
		FA	105	2	10 14 8 17 12			
Spontaneous tumor rate 11% in ctrl.		-	Total	-	4 9 1 1 7			
THYROID(S)	(50)	FA	67	1	0 1 0 0 0	0.9614	0.9464	0.9479
THYROID(S) BENIGN TUMOR F	(70)	FA	67	2	54 57 55 57 57			
		FA	76	1	0 0 0 1 0			
		FA	76	2	54 55 52 54 53			
		FA	92	1	0 1 0 0 0			
		FA	92	2	48 50 44 47 52			
		FA	103	1	0 1 0 0 0			
		FA	103	2	40 39 36 43 40			
		FA	104	1	2 2 0 0 1			
		FA	104	2	33 32 30 38 34			
		FA	105	1	0 1 0 0 0			
		FA	105	2	12 13 8 17 15			
Spontaneous tumor rate 7% in ctrl.		-	Total	-	2 6 0 1 1			
THYROID(S)	(50)	FA	103	1	1 0 0 0 0	0.6645	0.6323	0.6438
THYROID(S) MALIGNANT TUMO	(71)	FA	103	2	39 40 36 43 40			
		FA	104	1	0 0 0 1 0			
		FA	104	2	35 34 30 37 35			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	1 0 0 1 0			
THYROID(S)	(50)	FA	105	1	0 1 0 0 0	1.0000	0.8316	0.8421
THYROID(S) MALIGNANT TUMO	(72)	FA	105	2	12 13 8 17 15			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 1 0 0 0			
CECUM	(6)	FA	103	1	0 0 0 0 1	0.2010	0.0413	0.0454
CECUM MALIGNANT TUMOR SCH	(10)	FA	103	2	40 40 36 43 39			
Spontaneous tumor rate LE 1% in ctrl.		-	Total	-	0 0 0 0 1			

(End of File)

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Table 10b

Analysis of Carcinogenic Potential in **Female Rat**
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: November 7, 1997 (12:15)
Source: C:\TOLTERODINE\p9350f.dat

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 5 10 20)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
ADRENAL(S)	(1	) FA	72	1	0 1 0 0 0	0.6334	0.5635	0.5779
ADRENAL(S) BENIGN TUMOR C	(1	) FA	72	2	49 52 56 54 52			
		FA	105	1	1 0 0 0 1			
		FA	105	2	19 25 18 16 27			
Spontaneous tumor rate 2% in ctrl. - Total				-	1 1 0 0 1			
ADRENAL(S)	(1	) FA	104	1	0 1 0 0 0	1.0000	0.9032	0.9106
ADRENAL(S) BENIGN TUMOR P	(2	) FA	104	2	29 33 26 25 34			
		FA	105	1	0 1 0 0 0			
		FA	105	2	20 24 18 16 28			
Spontaneous tumor rate 2% in ctrl. - Total				-	0 2 0 0 0			
ADRENAL(S)	(1	) IN	92-102	1	0 0 0 0 1	0.4739	0.4312	0.4460
ADRENAL(S) MALIGNANT TUMO	(3	) IN	92-102	2	9 9 10 15 11			
		FA	81	1	0 1 0 0 0			
		FA	81	2	44 48 46 49 48			
		FA	105	1	0 0 1 0 0			
		FA	105	2	20 25 17 16 28			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 1 0 1			
HEMOPOIETIC SYST	(16	) IN	103-105	1	0 0 0 1 0	0.3986	0.3591	0.3832
HEMOPOIETIC SYST MALIGNAN	(14	) IN	103-105	2	29 34 26 24 34			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 1 0			
HEMOPOIETIC SYST	(16	) IN	53-78	1	0 0 0 0 1	0.2645	0.1984	0.2104
HEMOPOIETIC SYST MALIGNAN	(15	) IN	53-78	2	9 11 11 11 6			
		IN	79-91	1	0 0 0 1 0			
		IN	79-91	2	9 6 11 8 4			
		IN	92-102	1	0 1 0 0 0			
		IN	92-102	2	9 8 10 15 12			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 1 0 1 1			
HEMOPOIETIC SYST	(16	) IN	0-52	1	0 0 1 0 1	0.3895	0.3605	0.3724
HEMOPOIETIC SYST MALIGNAN	(17	) IN	0-52	2	4 0 1 0 2			
		IN	53-78	1	0 0 1 0 0			
		IN	53-78	2	9 11 10 11 7			
		FA	105	1	0 0 1 0 0			
		FA	105	2	20 25 17 16 28			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 3 0 1			
ILEUM	(17	) FA	102	1	0 0 0 1 0	0.3841	0.3457	0.3700
ILEUM BENIGN TUMOR LEIOMY	(18	) FA	102	2	32 37 32 27 35			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 1 0			
KIDNEY(S)	(19	) FA	106	1	0 0 0 0 1	0.4400	0.1443	0.1572
KIDNEY(S) MALIGNANT TUMOR	(20	) FA	106	2	1 8 2 3 10			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 0 1			
LIVER	(20	) FA	81	1	0 0 1 0 0	0.2232	0.1761	0.1880
LIVER BENIGN TUMOR HEPATO	(22	) FA	81	2	44 49 45 49 48			
		FA	105	1	0 0 0 0 1			
		FA	105	2	20 25 18 16 27			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 1 0 1			
LIVER	(20	) FA	106	1	0 0 0 1 0	0.5600	0.5176	0.5396
LIVER MALIGNANT TUMOR HEP	(24	) FA	106	2	1 8 2 2 11			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 1 0			
MAMMARY GLAND	(23	) IN	103-105	1	0 0 0 0 1	0.2297	0.0513	0.0584
MAMMARY GLAND BENIGN TUMO	(27	) IN	103-105	2	29 34 26 25 33			
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0 0 0 0 1			
MAMMARY GLAND	(23	) IN	0-52	1	1 0 0 0 0	0.9976	0.9968	0.9969
MAMMARY GLAND BENIGN TUMO	(28	) IN	0-52	2	3 0 2 0 3			
		IN	53-78	1	1 1 5 0 0			
		IN	53-78	2	8 9 5 11 7			
		IN	79-91	1	2 1 3 3 2			
		IN	79-91	2	7 5 8 6 2			
		IN	92-102	1	3 3 2 9 1			
		IN	92-102	2	6 5 7 6 11			
		IN	103-105	1	15 18 10 6 10			

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