

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-771**

**STATISTICAL REVIEW(S)**

**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.

**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

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,

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.

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.

### 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).

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

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.

- (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.

### **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.

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.

Concur: Dr. Lin

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11/19/97

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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.

**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					Total
	CTRL1	CTRL2	LOW	MED	HIGH	
	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

Table 1b

## NUMBER OF ANIMALS DIED

Species: Mouse  
Sex: Female

	Treatment Group					Total Count
	CTRL1	CTRL2	LOW	MED	HIGH	
	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

APPEARS THIS WAY  
ON ORIGINAL

Table 2a

## INTERCURRENT MORTALITY RATES

Intercurrent Mortality Rates  
 Species: Mouse  
 Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died
Time(-wks)															
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

APPEARS THIS WAY  
 ON ORIGINAL

Table 2b

## INTERCURRENT MORTALITY RATES

Species: Mouse

Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)															
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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ON ORIGINAL

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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ON ORIGINAL

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

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 PAPILOMA
28	SKIN MALIGNANT TUMOR FIBROLIPOSARCOMA
29	SKIN MALIGNANT TUMOR FIBROSARCOMA
30	STOMACH BENIGN TUMOR SQUAMOUS PAPILOMA
31	SUBMAXILL. S.G. MALIGNANT TUMOR SALIVARY ADENOCARCINOMA
32	TONGUE BENIGN TUMOR SQUAMOUS PAPILOMA
33	URINARY BLADDER BENIGN TUMOR LEIOMYOMA
34	URINARY BLADDER BENIGN TUMOR TRANSITIONAL CELL PAPILOMA
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

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 TIME TYPES STRATA	ROW NO.	2xC CONTINGENCY -----TABLE-----	EXACT PROB	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 rate 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			

Table 5a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)	-PR (STATISTIC.GE.OBSERVED)
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\9359F.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	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
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 TUMOR	(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			

Table 5b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC -----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				

Table 5b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)	-PR (STATISTIC. GE. OBSERVED)
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					Total
	CTRL1	CTRL2	LOW	MED	HIGH	
	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					Total Count
	CTRL1	CTRL2	LOW	MED	HIGH	
	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

APPEARS THIS WAY  
ON ORIGINAL

Table 7a

## INTERCURRENT MORTALITY RATES

Species: Rat

Sex: Male

Time(- wks)	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died
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

APPEARS THIS WAY  
ON ORIGINAL

Table 7b

## INTERCURRENT MORTALITY RATES

Species: Rat

Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	No. RI-sk	Cumu Pct. Died	No. Died	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

APPEARS THIS WAY  
ON ORIGINAL

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

APPEARS THIS WAY  
ON ORIGINAL

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

APPEARS THIS WAY  
ON ORIGINAL

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(S)
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

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

**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

APPEARS THIS WAY  
ON ORIGINAL

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	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
ADRENAL(S)	(1	) FA 97	1	0 2 0 0 0			
ADRENAL(S) BENIGN TUMOR C	(1	) FA 97	2	46 46 42 47 47	1.0000	0.9649	0.9666
		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			

Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)	-PR (STATISTIC. GE. OBSERVED)
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 TUMOR	(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				

Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)	-PR (STATISTIC.GE.OBSERVED)
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				

Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)	-PR (STATISTIC.GE.OBSERVED)				
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 KERATO	(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 SQUAMO	(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								

Table 10a (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 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)

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 TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLE	EXACT PROB	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
ADRENAL(S)	(1	) FA 72	1	0 1 0 0 0			
ADRENAL(S) BENIGN TUMOR C	(1	) FA 72	2	49 52 56 54 52	0.6334	0.5635	0.5779
		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			

Table 10b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLE	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)
		IN 103-105	2	13 16 16 18 24			
		FA 75	1	0 1 0 0 0			
		FA 75	2	49 50 50 53 51			
		FA 93	1	0 0 1 0 0			
		FA 93	2	38 43 35 40 46			
		FA 101	1	0 1 0 0 0			
		FA 101	2	32 37 32 31 37			
		FA 105	1	1 0 0 1 0			
		FA 105	2	19 25 18 15 28			
Spontaneous tumor rate 40%		in ctrl. - Total	-	23 25 21 19 13			
MAMMARY GLAND	(23	) IN 92-102	1	0 0 1 0 0	0.8607	0.8263	0.8379
MAMMARY GLAND BENIGN TUMO	(29	) IN 92-102	2	9 9 9 15 12			
		IN 103-105	1	1 0 0 0 0			
		IN 103-105	2	28 34 26 25 34			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	1 0 1 0 0			
MAMMARY GLAND	(23	) IN 103-105	1	1 0 0 0 0	1.0000	0.8187	0.8350
MAMMARY GLAND BENIGN TUMO	(30	) IN 103-105	2	28 34 26 25 34			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	1 0 0 0 0			
MAMMARY GLAND	(23	) IN 0-52	1	1 0 0 0 0	0.7098	0.6971	0.7001
MAMMARY GLAND MALIGNANT T	(31	) IN 0-52	2	3 0 2 0 3			
		IN 53-78	1	2 4 5 2 0			
		IN 53-78	2	7 7 5 9 7			
		IN 79-91	1	1 1 3 2 1			
		IN 79-91	2	8 5 8 7 3			
		IN 92-102	1	3 1 2 3 5			
		IN 92-102	2	6 8 7 11 7			
		IN 103-105	1	13 8 3 11 8			
		IN 103-105	2	16 26 23 14 26			
		FA 93	1	0 0 1 0 0			
		FA 93	2	38 43 35 40 46			
		FA 95	1	0 0 0 1 0			
		FA 95	2	37 41 34 36 43			
Spontaneous tumor rate 28%		in ctrl. - Total	-	20 14 14 19 14			
OVARIES	(26	) FA 104	1	0 1 0 0 0	1.0000	0.8187	0.8350
OVARIES BENIGN TUMOR GRAN	(33	) FA 104	2	29 33 26 25 34			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 1 0 0 0			
OVARIES	(26	) FA 73	1	0 0 0 0 1	0.2016	0.0424	0.0488
OVARIES BENIGN TUMOR MIXE	(34	) FA 73	2	49 51 52 54 51			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 0 0 1			
OVARIES	(26	) FA 103	1	0 0 1 0 0	0.4914	0.4727	0.4907
OVARIES MALIGNANT TUMOR T	(35	) FA 103	2	31 35 27 25 35			
		FA 104	1	0 0 0 1 0			
		FA 104	2	29 34 26 24 34			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 1 1 0			
PANCREAS	(27	) FA 97	1	0 1 0 0 0	1.0000	0.9065	0.9139
PANCREAS BENIGN TUMOR ISL	(36	) FA 97	2	35 39 34 34 42			
		FA 100	1	0 1 0 0 0			
		FA 100	2	32 38 32 32 38			
Spontaneous tumor rate 2%		in ctrl. - Total	-	0 2 0 0 0			
PANCREAS	(27	) FA 101	1	0 0 0 0 1	0.2176	0.0472	0.0540
PANCREAS MALIGNANT TUMOR	(38	) FA 101	2	32 38 32 31 36			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 0 0 1			
PARATHYROID(S)	(28	) FA 80	1	1 0 0 0 0	1.0000	0.9491	0.9528
PARATHYROID(S) BENIGN TUM	(39	) FA 80	2	43 48 44 48 50			
		FA 105	1	0 2 0 0 0			
		FA 105	2	19 23 18 16 28			
Spontaneous tumor rate 3%		in ctrl. - Total	-	1 2 0 0 0			
BONE	(3	) IN 79-91	1	0 1 0 0 0	1.0000	0.8257	0.8458
BONE MALIGNANT TUMOR CHON	(5	) IN 79-91	2	9 5 11 9 4			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 1 0 0 0			
PERITONEAL CAV.	(31	) IN 79-91	1	0 0 1 0 0	0.6154	0.5497	0.5817
PERITONEAL CAV. MALIGNANT	(40	) IN 79-91	2	9 6 10 9 4			
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 1 0 0			

Table 10b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLE	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)	=PR (STATISTIC.GE.OBSERVED)
PITUITARY	(32	) IN 0-52	1	1 0 0 0 0	0.9999	0.9998	0.9998	
PITUITARY BENIGN TUMOR AD	(42	) IN 0-52	2	2 0 2 0 2				
		IN 53-78	1	3 5 5 8 3				
		IN 53-78	2	5 3 2 2 3				
		IN 79-91	1	7 3 10 8 1				
		IN 79-91	2	2 3 0 0 3				
		IN 92-102	1	8 6 6 10 6				
		IN 92-102	2	0 0 1 3 4				
		FA 43	1	1 0 0 0 0				
		FA 43	2	56 60 58 60 57				
		FA 63	1	0 1 0 0 0				
		FA 63	2	53 56 58 58 56				
		FA 64	1	0 0 0 0 1				
		FA 64	2	52 56 58 58 55				
		FA 69	1	0 1 1 0 0				
		FA 69	2	51 54 56 56 54				
		FA 72	1	0 1 2 0 0				
		FA 72	2	49 52 54 54 52				
		FA 74	1	0 0 0 1 0				
		FA 74	2	49 51 52 53 51				
		FA 75	1	0 0 1 0 0				
		FA 75	2	49 51 50 53 51				
		FA 88	1	0 0 1 0 0				
		FA 88	2	40 44 37 44 47				
		FA 91	1	0 0 0 1 0				
		FA 91	2	38 43 36 41 46				
		FA 93	1	0 0 1 0 0				
		FA 93	2	38 43 35 40 46				
		FA 96	1	1 0 0 1 0				
		FA 96	2	36 41 34 35 43				
		FA 99	1	0 0 0 1 0				
		FA 99	2	32 39 32 33 40				
		FA 100	1	0 0 0 0 1				
		FA 100	2	32 39 32 32 37				
		FA 101	1	0 1 0 0 1				
		FA 101	2	32 37 32 31 36				
		FA 102	1	0 2 2 0 0				
		FA 102	2	32 35 30 28 35				
		FA 104	1	9 8 8 7 6				
		FA 104	2	20 26 18 18 28				
		FA 105	1	16 16 11 11 9				
		FA 105	2	4 9 7 5 19				
		FA 106	1	0 7 0 3 5				
		FA 106	2	1 1 2 0 6				
Spontaneous tumor rate 81%		in ctrl. - Total	-	46 51 48 51 33				
PITUITARY	(32	) IN 53-78	1	2 2 0 0 0	0.9727	0.9502	0.9527	
PITUITARY MALIGNANT TUMOR	(43	) IN 53-78	2	6 9 11 11 7				
		IN 79-91	1	1 1 0 0 0				
		IN 79-91	2	8 5 11 9 4				
		FA 105	1	1 0 0 0 1				
		FA 105	2	19 25 18 16 27				
Spontaneous tumor rate 6%		in ctrl. - Total	-	4 3 0 0 1				
PLEURAL CAVITY	(33	) FA 102	1	0 0 0 1 0	0.3841	0.3457	0.3700	
PLEURAL CAVITY BENIGN TUMOR	(44	) FA 102	2	32 37 32 27 35				
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 0 1 0				
RECTUM	(35	) FA 106	1	0 0 0 0 1	0.4400	0.1443	0.1572	
RECTUM BENIGN TUMOR ADENO	(46	) FA 106	2	1 8 2 3 10				
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 0 0 1				
RECTUM	(35	) FA 105	1	0 0 1 1 0	0.5287	0.5049	0.5222	
RECTUM BENIGN TUMOR FIBRO	(47	) FA 105	2	20 25 17 15 28				
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 1 1 0				
SKELETAL MUSCLE	(38	) IN 92-102	1	0 0 0 1 0	0.4909	0.3938	0.4199	
SKELETAL MUSCLE MALIGNANT	(49	) IN 92-102	2	9 9 10 14 12				
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 0 0 1 0				
SKIN	(39	) FA 104	1	0 1 0 0 0	1.0000	0.8187	0.8350	
SKIN BENIGN TUMOR BASAL C	(50	) FA 104	2	29 33 26 25 34				
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 1 0 0 0				
SKIN	(39	) IN 53-78	1	0 1 0 0 0	1.0000	0.8180	0.8366	
SKIN BENIGN TUMOR FIBROMA	(51	) IN 53-78	2	9 10 10 11 7				
Spontaneous tumor rate LE 1%		in ctrl. - Total	-	0 1 0 0 0				

Table 10b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)	-PR (STATISTIC.GE.OBSERVED)
SKIN	(39	) IN 103-105	1	0 1 0 0 0	1.0000	0.8187	0.8350	
SKIN BENIGN TUMOR FIBROUS	(52	) IN 103-105	2	29 33 26 25 34				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	0 1 0 0 0				
SKIN	(39	) IN 103-105	1	0 1 1 0 0	0.8205	0.7998	0.8122	
SKIN BENIGN TUMOR LIPOMA	(55	) IN 103-105	2	29 33 25 25 34				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	0 1 1 0 0				
SKIN	(39	) IN 103-105	1	0 0 0 1 0	0.3986	0.3591	0.3832	
SKIN BENIGN TUMOR SQUAMO	(57	) IN 103-105	2	29 34 26 24 34				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	0 0 0 1 0				
SKIN	(39	) IN 53-78	1	0 0 1 0 0	0.8465	0.7812	0.7968	
SKIN MALIGNANT TUMOR FIBR	(58	) IN 53-78	2	9 11 9 11 7				
		IN 79-91	1	1 0 0 0 0				
		IN 79-91	2	7 6 11 9 4				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	1 0 1 0 0				
SKIN	(39	) IN 0-52	1	1 0 0 0 0	0.6829	0.6743	0.6873	
SKIN MALIGNANT TUMOR SCHW	(61	) IN 0-52	2	3 0 2 0 3				
		IN 53-78	1	0 0 0 1 0				
		IN 53-78	2	9 11 10 10 7				
		IN 103-105	1	0 0 1 0 0				
		IN 103-105	2	29 34 25 25 34				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	1 0 1 1 0				
SKIN	(39	) IN 103-105	1	0 1 0 0 0	1.0000	0.8187	0.8350	
SKIN MALIGNANT TUMOR SQUA	(62	) IN 103-105	2	29 33 26 25 34				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	0 1 0 0 0				
SPLEEN	(43	) FA 105	1	0 1 0 0 0	1.0000	0.8233	0.8388	
SPLEEN BENIGN TUMOR HEMAN	(64	) FA 105	2	20 24 18 16 28				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	0 1 0 0 0				
STOMACH	(45	) FA 104	1	0 0 0 1 0	0.3986	0.3591	0.3832	
STOMACH BENIGN TUMOR SQUA	(66	) FA 104	2	29 34 26 24 34				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	0 0 0 1 0				
THYROID(S)	(50	) FA 70	1	0 0 0 0 1	0.2740	0.2548	0.2591	
THYROID(S) BENIGN TUMOR C	(69	) FA 70	2	51 54 56 56 53				
		FA 75	1	0 1 0 1 0				
		FA 75	2	49 50 51 52 51				
		FA 84	1	1 0 0 0 0				
		FA 84	2	41 46 42 46 47				
		FA 86	1	0 0 0 1 0				
		FA 86	2	40 46 40 44 47				
		FA 88	1	0 0 1 0 0				
		FA 88	2	40 44 37 44 47				
		FA 96	1	1 0 0 0 0				
		FA 96	2	36 41 34 36 43				
		FA 98	1	0 0 0 0 1				
		FA 98	2	33 39 32 34 40				
		FA 103	1	0 1 1 0 0				
		FA 103	2	31 34 27 25 35				
		FA 104	1	1 2 0 1 0				
		FA 104	2	28 32 26 24 34				
		FA 105	1	0 1 1 0 3				
		FA 105	2	20 24 17 16 25				
		FA 106	1	0 1 0 0 3				
		FA 106	2	1 7 2 3 8				
Spontaneous tumor rate 8% in ctrl.	-	Total	-	3 6 3 3 8				
THYROID(S)	(50	) FA 71	1	0 0 0 1 0	0.7103	0.6946	0.7076	
THYROID(S) BENIGN TUMOR F	(70	) FA 71	2	49 54 56 55 53				
		FA 78	1	1 0 0 0 0				
		FA 78	2	47 49 48 49 51				
		FA 105	1	0 0 1 0 0				
		FA 105	2	20 25 17 16 28				
Spontaneous tumor rate LE 1% in ctrl.	-	Total	-	1 0 1 1 0				
UTERUS	(54	) FA 104	1	0 0 1 0 0	0.9655	0.9492	0.9518	
UTERUS BENIGN TUMOR FIBRO	(73	) FA 104	2	29 34 25 25 34				
		FA 105	1	3 1 0 0 0				
		FA 105	2	17 24 18 16 28				
		FA 106	1	0 0 0 1 0				
		FA 106	2	1 8 2 2 11				
Spontaneous tumor rate 3% in ctrl.	-	Total	-	3 1 1 1 0				

Table 10b (Continued)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC_CONTINGENCY -----TABLE-----	EXACT PROB	ASYMP TOTIC	ASYMP (CONTI NUITY CORR)	-PR (STATISTIC.GE.OBSERVED)
UTERUS	(54	) FA 105	1	0 0 0 0 1	0.2617	0.0638	0.0718	
UTERUS BENIGN TUMOR GRANU	(74	) FA 105	2	20 25 18 16 27				
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 0 0 0 1				
UTERUS	(54	) FA 81	1	0 1 0 0 0	1.0000	0.8286	0.8450	
UTERUS MALIGNANT TUMOR LE	(75	) FA 81	2	44 48 46 49 48				
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 1 0 0 0				
UTERUS	(54	) IN 0-52	1	0 0 0 0 1	0.3052	0.2519	0.2639	
UTERUS MALIGNANT TUMOR SC	(76	) IN 0-52	2	4 0 2 0 2				
		IN 53-78	1	1 0 0 0 0				
		IN 53-78	2	8 11 11 10 7				
		FA 75	1	0 0 0 1 0				
		FA 75	2	49 51 51 52 51				
Spontaneous tumor rate LE 1% in ctrl. - Total			-	1 0 0 1 1				
UTERUS	(54	) FA 106	1	0 1 0 0 0	1.0000	0.8748	0.8859	
UTERUS MALIGNANT TUMOR SQ	(77	) FA 106	2	1 7 2 3 11				
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 1 0 0 0				
VAGINA	(55	) FA 105	1	0 0 0 1 1	0.0721	0.0471	0.0506	
VAGINA BENIGN TUMOR FIBRO	(78	) FA 105	2	20 25 18 15 27				
		FA 106	1	0 0 0 0 1				
		FA 106	2	1 8 2 3 10				
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 0 0 1 2				
DUODENUM	(8	) IN 92-102	1	0 0 1 0 0	0.6667	0.6481	0.6731	
DUODENUM MALIGNANT TUMOR	(11	) IN 92-102	2	9 9 9 15 11				
Spontaneous tumor rate LE 1% in ctrl. - Total			-	0 0 1 0 0				

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