HFD-550 Cook

STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)

NDA #: 21-042

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APPLICANT: Merck Research Laboratories

NAME OF DRUG: VIOXX™ Tablets

DOCUMENTS REVIEWED: Volumes 52.28 through 52.34 of IND 46,894. Data on Floppy Diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Susan D. Wilson, Ph.D. (HFD-550).

I. BACKGROUND

In this submission, a total of 3 animal carcinogenicity studies were included:

TT#95-076-0: Rat Carcinogenicity Study (VIOXX™Dose: 2,5,8 mg/kg/day)
TT#96-603-0: Mouse Carcinogenicity Study (VIOXX™Dose: 5,10,20,30 mg/kg/day)
TT#96-605-0: Mouse Carcinogenicity Study (VIOXX™Dose: 60,100,300 mg/kg/day).

These three studies were conducted to investigate the oncogenic/carcinogenic potential of VIOXX™ when administered orally at selected dose levels for up to at least 104 weeks. All the studies had two similar control groups.

For separate control groups, this reviewer's independent analyses match up with those of the sponsor. All the analyses in this review are for the **"combined"** control groups.

II. THE RAT STUDY TT#95-076-0

IIa. Design

A 106-week study was conducted in rats to investigate the oncogenic/carcinogenic potential of VIOXX™ when administered orally. Three groups of 50 male and 50 female rats (Crl:CD®(SD)BR) were treated with VIOXX™ in concentrations of 2 (low), 5 (medium) and 8 (high) mg/kg/day; and, two control groups of 50 male and 50 female rats (Crl:CD®(SD)BR) received the placebo vehicle (0.5% [w/v] aqueous methylcellulose).

IIb. Reviewer's Analysis ("Combined" Control Groups)

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, FDA. 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 (male) and 1b (female) summarize the number of animals died at different time-intervals. Tables 2a and 2b summarize intercurrent mortality data for the male and female rats respectively. For the male as well as female rats, there appears to be an increased mortality in the high dose group as compared to other dose groups.

- Figures 1a and 1b depict the Kaplan-Meier survival distributions for males and females respectively. For the male rats (after 70 weeks) and female rats (after 20 weeks), there appears to be an increased mortality in the high dose group when compared to the other doses.

- Tables 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. The test of homogeneity and the test of linear trend yield non-significant results for the male rats. But for the female rats, Cox test yields a significant result ($p=0.0490$) whereas Kruskal-Wallis test yields a marginally significant result ($p=0.0548$).

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, 2, 5, and 8 for control, low, medium, and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 2,5 and 8 mg/kg of VIOXX™. The time-intervals used were 0-52, 53-78, 79-91, 92-103, 104 and beyond for males and 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 for males and females, respectively. 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 Rat Study TT#95-076-0

This reviewer's analyses show that for rat study, there is no statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in 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 rat carcinogenicity study in the light of the above guidelines.

Validity of Rat Study TT#95-076-0

Tables 2a and 2b contain mortality rates. Survival rates can be obtained by subtracting mortality rates from 100% for male and female rats 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. From the survival criteria mentioned above, it can be concluded that enough numbers of rats were exposed to the drug for a sufficient amount of time in both sexes.

The sponsor's Figure A-2 (for males, p. E-62, vol. 52.29) and Figure A-1 (for females, p. E-61, vol. 52.29) indicate that body weights for high-dose were very close to the controls throughout the study for males and females. From the weight-gain criteria mentioned above, it can be concluded that the high dose used (8 mg/kg/day) may be close to the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IId. Additional Statistical Analyses

At the request of the reviewing pharmacologist, two additional tumor analyses were performed for both sexes:

Analysis #1: hepatocellular adenoma and carcinoma for the liver
Analysis #2: adenoma and carcinoma for the pancreas islet.

The tumor analysis results for the above analyses are displayed in Table 17a (for males) and 17b (for females). No statistically significant positive linear trend was detected in the above analyses (shaded regions).

IIe. Summary of Rat Study TT#95-076-0

For the male rats, no statistically significant positive linear trend or increased mortality was detected in the treated groups when compared with the control. But for the female rats, Cox test yielded a significant result (p=0.0490) whereas Kruskal-Wallis test yielded a marginally significant result (p=0.0548).

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 rats were exposed to the drug for a sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used (8 mg/kg/day) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

III. THE MOUSE STUDY TT#96-603-0

IIIa. Design

A 106-week study was conducted in mice to investigate the oncogenic/carcinogenic potential of VIOXX™ when administered orally. Four groups of 50 male and 50 female mice (Crl:CD-1®(ICR)BR) were treated with VIOXX™ in concentrations of 5 (low), 10 (medium), 20 (high), and 30 (maximum) mg/kg/day; and, two control groups of 50 male and 50 female mice (Crl:CD-1®(ICR)BR) received the placebo vehicle (0.5% [w/v] aqueous methylcellulose).

IIIb. Reviewer's Analysis ("Combined" Control Groups)

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, FDA. 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 (male) and 6b (female) give the number of animals died at different time-intervals. Tables 7a and 7b summarize the intercurrent mortality data for the male and female mice respectively. For the male mice, in the time-intervals of 53-78 weeks, 79-91 weeks and 92-103 weeks, there appears to be an increased mortality in the high dose group as compared to other dose groups. For the female mice, in the time-interval of 92-103 weeks, more animals died in maximum dose group than in the other groups.

- Figures 2a and 2b depict the Kaplan-Meier survival distributions for males and females respectively. For the male mice, after 60 weeks, there appears to be an increased mortality in the high dose group when compared to the other doses. For the female mice, the curves for different dose groups intertwine each other suggesting that there is no significant difference between their survival patterns. The test of homogeneity yields

significant results for the male mice and non-significant results for the female mice (Tables 8a and 8b in the Appendix).

- Tables 8a and 8b display the p-values of the test of homogeneity and of positive linear trends for males and females, respectively, 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 yield significant results for the male mice which confirm the graphical findings of Figure 2a.

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. The scores used were 0, 5, 10, 20 and 30 for the control, low, medium, high and maximum dose groups respectively. This was done in order to reflect the actual dose levels of 0, 5, 10, 20 and 30 mg/kg of VIOXX™. The time-intervals used were 0-52, 53-78, 79-91, 92-103, 104 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 for males and females, respectively. 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.

IIIc. Evaluation of Validity of the Design of Mouse Study TT#96-603-0

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 mice carcinogenicity study in the light of the above guidelines.

Validity of Mouse Study TT#96-603-0

Tables 7a and 7b contain mortality rates. Survival rates can be obtained by subtracting mortality rates from 100% for male and female rats 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. From the survival criteria mentioned above, it can be concluded that enough numbers of mice were exposed to the drug for a sufficient amount of time in both sexes.

The sponsor's Figure 2 (for males, p. E-731, vol. 52.30) and Figure 1 (for females, p. E-730, vol. 52.30) indicate that body weights for maximum dose were very close to the controls throughout the study for males and females. From the weight-gain criteria mentioned above, it can be concluded that the maximum dose used (30 mg/kg/day) may be close to the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IIId. Additional Statistical Analyses

At the request of the reviewing pharmacologist, four additional tumor analyses were performed for both sexes:

Analysis #1: hepatocellular adenoma and carcinoma for the liver
Analysis #2: adenoma and adenocarcinoma for the lung
Analysis #3: leiomyoma and leiomyosarcoma for the uterus
Analysis #4: all the following organ-tumors combined

Large intestine—leiomyosarcoma
Liver—hemangiosarcoma
Uterus—hemangiosarcoma and leiomyosarcoma
Uterus endometrial stroma—sarcoma
Testis—hemangiosarcoma
Skin—fibrosarcoma, hemangiosarcoma,osteosarcoma
Spleen—hemangiosarcoma
Bone cranial and facial bones—osteosarcoma
Eye—rhabdomyosarcoma
Tail—rhabdomyosarcoma
Primary Site Undetermined– hemangiosarcoma,osteosarcoma and histiocytic sarcoma.

The tumor analysis results for the first three analyses are displayed in Table 18a (for males) and Table 18b (for females) and for the fourth analysis in Table 19a (for males) and Table 19b (for females). No statistically significant positive linear trend was detected in the above analyses (shaded regions) except for uterine leiomyoma and leiomyosarcoma for females. The significant results are produced below.

Female Mice			Tumor Rate					Trend Test p-value
Organ	Tumor Name	Tumor Type	Control N=100	Low N=50	Medium N=50	High N=50	Maxi N=50	
Uterus	Leiomyoma and leiomyosarcoma	Mixed	0	2	1	6	2	0.0167

IIIe. Summary of Mouse Study TT#96-603-0

No statistically significant positive linear trend or increased mortality in the treated groups when compared with the control was detected in either sex.

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. But, when uterine leiomyoma and leiomyosarcoma were combined at the reviewing pharmacologist's request, a statistically significant positive linear trend was detected.

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 be concluded that the maximum dose used (30 mg/kg/day) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IV. THE MOUSE STUDY TT#96-605-0

IVa. Design

A 104-week study was conducted in mice to investigate the oncogenic/carcinogenic potential of VIOXX™ when administered orally. Three groups of 50 male and 50 female mice (Crl:CD-1®(ICR)BR) were treated with VIOXX™ in concentrations of 60 (low), 100 (medium), and 300 (high) mg/kg/day; and, two control groups of 50 male and 50 female mice (Crl:CD-1®(ICR)BR) received the placebo vehicle (0.5% [w/v] aqueous methylcellulose).

Due to high drug-related mortality rates, the 100 and 300 mg/kg/day groups were terminated in Drug Week 72 and the animals discarded without further examination; for the same reason, males from the 60 mg/kg/day were sacrificed early in Drug Week 89, together with the male control groups and underwent a routine necropsy and microscopic examination.

IVb. Reviewer's Analysis ("Combined" Control Groups)

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, FDA. 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 12a (male) and 12b (female) give the number of animals died at different time-intervals. Tables 13a and 13b summarize the intercurrent mortality data for the male and female mice respectively. For the male mice, in the time-intervals of 0-52 weeks, 53-78 weeks, and 79-88 weeks, there is a very high mortality in the low dose group as compared to the control. For the female mice, there is an increasing mortality with time in both the groups.

- Figures 3a and 3b depict the Kaplan-Meier survival distributions for males and females respectively. For the male mice, there is an increased mortality in the low dose group when compared to the control. For the female mice, the curves for both the groups intertwine each other suggesting that there is no significant difference between their survival patterns. The test of homogeneity yields highly significant results for the male mice and non-significant results for the female mice (Tables 14a and 14b in the Appendix).

- Tables 14a and 14b display the p-values of the test of homogeneity and of positive linear trends for males and females, respectively, 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 yield significant results for the male mice which confirm the graphical findings of Figure 3a.

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 15 (Part I) displays selected organs and organ codes. Table 15 (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 and 60 for the control and low dose groups respectively. This was done in order to reflect the actual dose levels of 0 and 60 mg/kg of VIOXX™. The time-intervals used were 0-52, 53-78, 79-88, 89 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 16a and 16b describe the p-values for the test of trend based on the tumor data for males and females, respectively. 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.

IVc. Additional Statistical Analyses

At the request of the reviewing pharmacologist, two additional tumor analyses were performed for both sexes:

Analysis #1: adenoma and adenocarcinoma for the lung
Analysis #2: adenoma and adenocarcinoma for the eye harderian gland.

The tumor analysis results for the above analyses are displayed in Table 20a (for males) and 20b (for females). No statistically significant positive linear trend was detected in the above analyses (shaded regions).

IVd. Summary of Mouse Study TT#96-605-0

Daily oral administration of VIOXX™ to mice at the dose levels of 60, 100, and 300 mg/kg/day resulted in drug-related deaths. Due to high drug-related mortality rates, the 100 and 300 mg/kg/day groups were terminated in Drug Week 72 and the animals discarded without further examination; for the same reason, males from the 60 mg/kg/day were sacrificed early in Drug Week 89, together with the male control groups and underwent a routine necropsy and microscopic examination.

For the male (with the data up to Week 89 only) and female mice, there was no statistically significant difference in the tumor-incidence between the control group and the VIOXX™ 60 mg/kg/day group.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the 60 mg/kg/day group (with the data up to 89 weeks for males) when compared with the control.

IV. SUMMARY

Summary of the Rat Study TT#95-076-0

For the male rats, no statistically significant positive linear trend or increased mortality was detected in the treated groups when compared with the control. But for the female rats, Cox test yielded a significant result (p=0.0490) whereas Kruskal-Wallis test yielded a marginally significant result (p=0.0548).

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 rats were exposed to the drug for a sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used (8 mg/kg/day) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

Summary of the Mouse Study TT#96-603-0

No statistically significant positive linear trend or increased mortality in the treated groups when compared with the control was detected in either sex.

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. But, when uterine leiomyoma and leiomyosarcoma were combined at the reviewing pharmacologist's request, a statistically significant positive linear trend was detected.

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 be concluded that the maximum dose used (30 mg/kg/day) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

Summary of Mouse Study TT#96-605-0

Daily oral administration of VIOXX™ to mice at the dose levels of 60, 100, and 300 mg/kg/day resulted in drug-related deaths. Due to high drug-related mortality rates, the 100 and 300 mg/kg/day groups were terminated in Drug Week 72 and the animals discarded without further examination; for the same reason, males from the 60 mg/kg/day were sacrificed early in Drug Week 89, together with the male control groups and underwent a routine necropsy and microscopic examination.