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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAY OF CLONITRALID
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of clonitralid conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of clonitralid was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed by Dr. D. A. Banas (3) and Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6), using

methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

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The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay for possible carcinogenicity of clonitralid was conducted using Osborne-Mendel rats and B6C3F1 mice. Clonitralid was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The time-weighted average high and low dietary concentrations of clonitralid were, respectively, 28,433 and 14,216 ppm for rats and 549 and 274 ppm for mice. After a 78-week period of compound administration, there was an additional observation period of 32 to 33 weeks for rats and 13 to 14 weeks for mice.

Adequate numbers of male rats, female rats, and female mice survived long enough to be at risk from late-developing tumors. Because of inadequate survival among male mice, however, results obtained from observation of the male mouse groups cannot be considered conclusive.

The incidences of mammary adenocarcinomas in treated female rats were not significantly higher than the incidences observed in control female rats. However, the incidences of this lesion in dosed female rats were greater than or equal to 22 percent, while the highest incidence observed in 15 control groups at this laboratory was only 10 percent with a mean incidence of 2.6 percent. The occurrence in high dose female rats (2/45) of carcinomas in the glandular portion of the stomach with metastases to other sites was not statistically significant. This incidence, however, is much greater than the historical control incidence and suggests an association between administration of clonitralid and the development of these tumors.

No statistically significant increased tumor incidences were observed among male rats or mice of either sex dosed with clonitralid.

Under the conditions of this bioassay, there was no convincing evidence that clonitralid was carcinogenic to Osborne-Mendel rats or to female B6C3F1 mice. Poor survival of male mice did not permit an evaluation of carcinogenicity in these animals.

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I. INTRODUCTION

Clonitralid (Figure 1) (NCI No. C00431), a powerful molluscicide and lamprey killer, was selected for bioassay by the National Cancer Institute because of the large potential for human exposure resulting from the direct application of the compound for control of sea lamprey larvae in tributaries to the Great Lakes (Menzie, 1977) and the widespread application of clonitralid for the control of water snails (Sturrock, 1974; Sturrock et al., 1974; Magendantz, 1974). The lack of data on the toxic effects of chronic exposure to clonitralid was an additional factor in the selection of this compound for testing.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide compound with 2-aminoethanol (1:1).* It is also called 2',5-dichloro-4'-nitrosalicylanilide compound with 2-aminoethanol (1:1); clonitralide; Bayer 25648; Bayer 73; and SR 73.

Clonitralid is used alone or in a mixture with 3-trifluoromethyl-4-nitrophenol sodium salt by the U.S. Fish and Wildlife Service in the Great Lakes sea lamprey (*Petromyzon marinus*) control program (Menzie, 1977). Sea lampreys, which become trapped in the lakes after gaining access in large numbers through canals with locks, have attacked and drastically reduced the large, and commercially important lake trout populations, at one point reducing the annual catch from 15 million

*The CAS registry number is 1420-04-8.

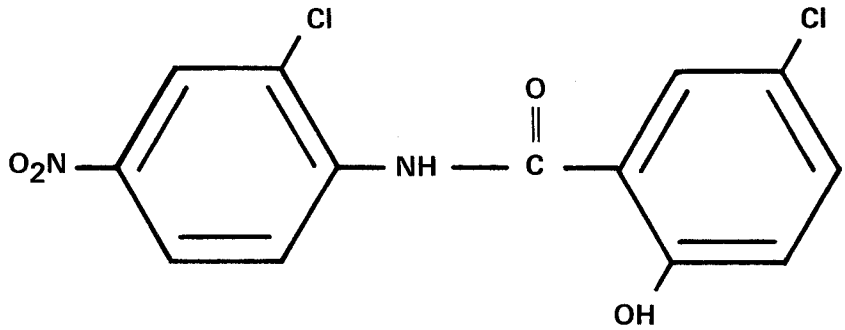


FIGURE 1
CHEMICAL STRUCTURE OF CLONITRALID

to 0.5 million pounds (Storer et al., 1972). Clonitralid is introduced in Great Lakes tributaries, in amounts which vary with the rate of flow of the streams, to eradicate the burrowing lamprey larvae (Menzie, 1977).

Clonitralid is used extensively for the control of water snails, especially in tropical areas (Farm Chemicals Handbook, 1976; Sturrock, 1974; Sturrock et al., 1974; Magendantz, 1974). These snails are intermediate hosts for blood and liver flukes, which produce schistosomiasis and fascioliasis, respectively, thereby constituting a significant health hazard (Farm Chemicals Handbook, 1976; Morris, 1976). The control of water snails by clonitralid is achieved, not only by direct introduction into the aqueous environment, but also by application of the compound to vegetation and soils (Sturrock, 1974; Sturrock et al., 1974). Clonitralid is extremely toxic to water snails, giving a total kill of mature *Australorbis glabratus* after 24 hours of exposure to concentrations as low as 0.1 ppm (Fox et al., 1966), and lowering populations of *Biomphalaria choanomphala* by 90 to 100 percent, under favorable conditions, when applied to lake and stream bottoms at a rate of 3.75 kg/ha (Magendantz, 1974).

Clonitralid has also been examined, with favorable results, for use as a fish toxicant in streams or impounded water (Farm Chemicals Handbook, 1976).

Specific production figures for clonitralid are not available. Commercial production (in excess of 1000 pounds or $1000 in value

annually) was last reported in 1975 by one U.S. company (Stanford Research Institute, 1976).

The potential for exposure to clonitralid is greatest for pest control workers, especially those who apply the compound as a spray. Workers in production facilities may also be exposed. The major route of population exposure is presumably dermal contact with or ingestion of treated water or ingestion of contaminated fish. Clonitralid levels in both cases are probably quite low because the high toxicity of the compound to fish and other nontarget organisms (Farm Chemicals Handbook, 1976) necessitates extremely low and well-controlled practicable concentrations. Toxic levels of clonitralid for a number of species of fish tested were well below 0.5 ppm (Farm Chemicals Handbook, 1976).

Clonitralid residues do not accumulate to a detectable degree in bananas when applied to the soil surrounding the plants at concentrations of 0.125 to 1.250 ppm (Sturrock et al., 1974), thus precluding ingestion when used in this manner. Clonitralid sprayed on vegetation, however, remained toxic to *Biomphalaria glabrata* for 8 weeks, and residues persisted in mud for over a year, in both cases under tropical conditions (Sturrock, 1974).

No data on the toxicity of this compound to humans are available. In contrast to the efficacy of clonitralid against mollusks, fish, and lampreys, experiments with rats have indicated a relatively low mammalian toxicity (Farm Chemicals Handbook, 1976).

II. MATERIALS AND METHODS

A. Chemicals

Technical-grade clonitralid (2',5-dichloro-4'-nitrosalicylanilide ethanolamine salt) was purchased from Chemagro Corporation, Kansas City, Missouri, and analyzed by Hazleton Laboratories, Inc., Vienna, Virginia. The experimentally determined melting point of 192° to 200°C suggested the presence of impurities due to the wide spread and difference from the reported literature value of 216°C. Purity, determined by a colorimetric method (suggested by the manufacturer) utilizing ultraviolet absorbance at 416 nm, was shown to be greater than 90 percent. A similar chemical analysis was performed twelve months later. A change in the experimentally determined melting point (186° to 190°C) did suggest some change, although it cannot be ascertained whether this was attributable to alterations in the impurities, the major compound, or both. Colorimetry results of the second analysis were similar to those of the first.

Throughout this report the term clonitralid is used to represent this technical-grade material.

B. Dietary Preparation

The basal laboratory diet for treated and control animals consisted of Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinos) plus 2 percent Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) by weight. Fresh mixtures of clonitralid in corn oil were prepared each week and stored in the dark. The clonitralid mixtures

were incorporated into the appropriate amount of laboratory diet in a twin-shell blender fitted with an accelerator bar.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various dosed and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors, while mice were housed by sex in groups of ten in solid-bottom, polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips , Pine-wood Sawdust Company, Moonachie, New Jersey) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter, while fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food (Wayne Lab-Blox meal) and water were available ad libitum.

The clonitralid-dosed and control rats were housed in the same room with other rats receiving diets containing* dioxathion (78-34-2); mexacarbate (315-18-4); pentachloronitrobenzene (82-68-8); amitrole (61-82-5); nitrofen (1836-75-5); endosulfan (115-29-7); and trifluralin (1582-09-8).

All mice used in the dicofol study, including controls, were housed in the same room as other mice receiving diets containing trifluralin (1582-09-8); chlorobenzilate (510-15-6); dioxathion (78-34-2); sulfallate (95-06-7); p,p'-DDT (50-29-3); methoxychlor (72-43-5); p,p'-DDE (72-55-9); p,p'-TDE (72-54-8); dicofol (115-32-2); pentachloronitrobenzene (82-68-8); nitrofen (1836-75-5); endosulfan (115-29-7); mexacarbate (315-18-4); amitrole (61-82-5); acetylaminofluorene (53-96-3); and safrole (94-59-7).

*CAS registry numbers are given in parentheses.

E. Selection of Initial Concentration

In order to establish the maximum tolerated concentrations of clonitralid for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Clonitralid was premixed with a small amount of corn oil. This mixture was then incorporated into the laboratory diet and fed *ad libitum* to five of the six rat groups in concentrations of 2150, 4640, 10,000, 21,500, and 46,400 ppm. Five of the six mouse groups were given concentrations of 464, 1000, 2150, 4640, and 10,000 ppm. The sixth group of each species served as a control group, receiving only the mixture of corn oil and laboratory meal. The dosed dietary preparations were administered for a period of 6 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet.

A concentration inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent relative to controls was selected as the initial high concentration for the chronic study. When weight gain criteria were not applicable, mortality data alone were utilized.

At both 10,000 and 21,500 ppm, mean body weight depression was 17 percent in male rats. In female rats, mean body weight depression was 14 percent at 10,000 ppm, and 21 percent at 21,500 ppm. The initial high concentrations selected for male and female rats in the

chronic bioassay were 17,500 and 19,000 ppm, respectively. The high concentration actually used for rats of both sexes in the chronic bioassay was 18,250 ppm.

Mean body weight depression was first evident at a concentration of 464 ppm for both male and female mice. At that concentration mean body weight depression was 27 percent for the male mice and 14 percent for the female mice. At 1000 ppm, the mean body weight depression for male mice was 34 percent, and for female mice was 55 percent. The initial high concentration selected for both male and female mice in the chronic bioassay was 380 ppm.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, concentrations administered, duration of treated and untreated observation periods, and the time-weighted average concentrations) are summarized in Tables 1 and 2.

The treated and control rats were all approximately 6 weeks old at the time they were placed on test and all shared the same median date of birth. The concentrations of clonitralid initially utilized for male and female rats were 18,250 and 9125 ppm. Throughout this report those rats initially receiving the former concentration are referred to as the high dose groups, while those initially receiving the latter concentration are referred to as the low dose groups. In week 8, the high and low concentrations administered to the male and female rats were increased to 25,000 and 12,500 ppm, respectively.

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
CLONITRALID FEEDING EXPERIMENT

	INITIAL GROUP SIZE	CLONITRALID CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0	-	110	0
LOW DOSE	50	9,125	7		14,216
		12,500	8		
		15,000	63		
		0		32	
HIGH DOSE	50	18,250	7		28,433
		25,000	8		
		30,000	63		
		0		33	
FEMALE					
CONTROL	20	0	-	110	0
LOW DOSE	50	9,125	7		14,216
		12,500	8		
		15,000	63		
		0		33	
HIGH DOSE	50	18,250	7		28,433
		25,000	8		
		30,000	63		
		0		33	

[a]Concentrations given in parts per million.

[b]Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
CLONITRALID FEEDING EXPERIMENT

	INITIAL GROUP SIZE	CLONITRALID CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0	-	91	0
LOW DOSE	50	190	8		274
		225	15		
		300	55		
		0		13	
HIGH DOSE	50	380	8		549
		450	15		
		600	55		
		0		13	
FEMALE					
CONTROL	20	0	-	91	0
LOW DOSE	50	190	8		274
		225	15		
		300	55		
		0		14	
HIGH DOSE	50	380	8		549
		450	15		
		600	55		
		0		14	

[a]Concentrations given in parts per million.

[b]Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{\Sigma(\text{weeks receiving chemical})}$

In week 16, the dosages were again increased, to 30,000 ppm for the high dose male and female rats, and to 15,000 ppm for the low dose male and female rats. These concentrations were maintained for the remainder of the period of compound administration. After the period of 78 weeks, observation of all rats used in the chronic bioassay continued for an additional period of up to 33 weeks.

The treated and control mice were all approximately 6 weeks old at the time the experiment began and all shared the same median date of birth. The concentrations administered to male and female mice for the first 8 weeks were 380 and 190 ppm. Throughout this report those mice initially receiving the former concentration are referred to as the high dose groups, while those mice initially receiving the latter concentration are referred to as the low dose groups. In week 9, the high and low concentrations were increased to 450 and 225 ppm, respectively. In week 24, dosages were again increased, this time to 600 and 300 ppm for the high and low dose groups, respectively. These concentrations were maintained for the remainder of the 78-week period. Observation of all mice continued for up to 14 weeks after the period of compound administration.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for

the first 10 weeks and at monthly intervals thereafter. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

During the course of this bioassay several pathology protocols were in effect, each for different periods of time. The minimum protocol required that, if possible, certain tissues were to be taken and examined histopathologically from all control animals, from any animal in which a tumor was observed during gross examination, and from at least 10 grossly normal males and 20 grossly normal females from each treated group. In addition, any tissues showing gross abnormalities were to be taken and examined histopathologically. Under later protocols, some tissues were taken from additional dosed animals. The number of animals in each group from which a tissue was examined is indicated in Appendices A through D.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrified at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior

to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

Slides were prepared from the following tissues from selected animals: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, tunica vaginalis, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum,

1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary

tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from

the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

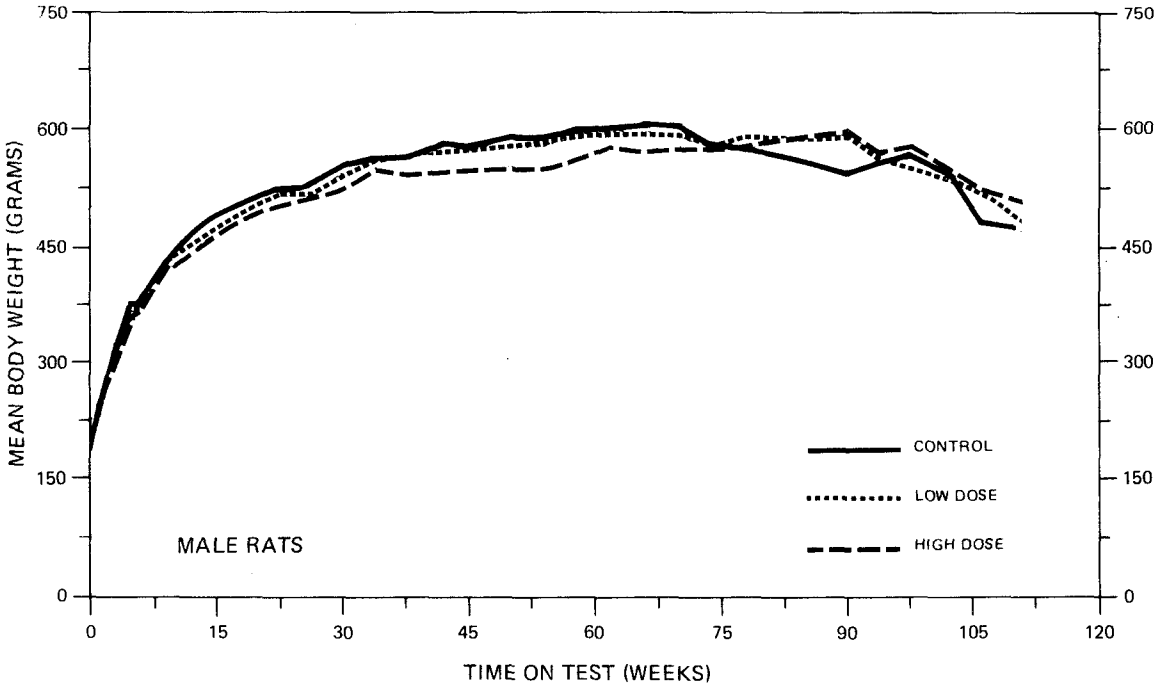
A. Body Weights and Clinical Observations

In treated females there was distinct, compound-related mean body weight depression when compared to controls. This was not, however, true for males (Figure 2).

For the duration of compound administration, appearance and behavior were generally comparable for all groups with the exception of slightly higher incidences of hunched appearance, abdominal urine stains, and/or rough fur in the treated rats when compared to the untreated controls. From cessation of compound administration to termination of the study, clinical signs were noted at comparable rates in control and treated animals. These signs included hunched appearance; abdominal urine stains; rough fur; body sores; cloudy, squinted, or reddened eyes with discharge or crust; and alopecia. As the animals aged, the incidence of these signs gradually increased in all groups. Respiratory signs characterized by labored respiration, wheezing and/or nasal discharge were observed at a low to moderate incidence during the study. During the last three months of the study, palpable subcutaneous nodules were observed at a greater frequency in the high dose male and female rats than in the other groups.

B. Survival

The estimated probabilities of survival for male and female rats in the control and clonitralid-dosed groups are shown in Figure 3.



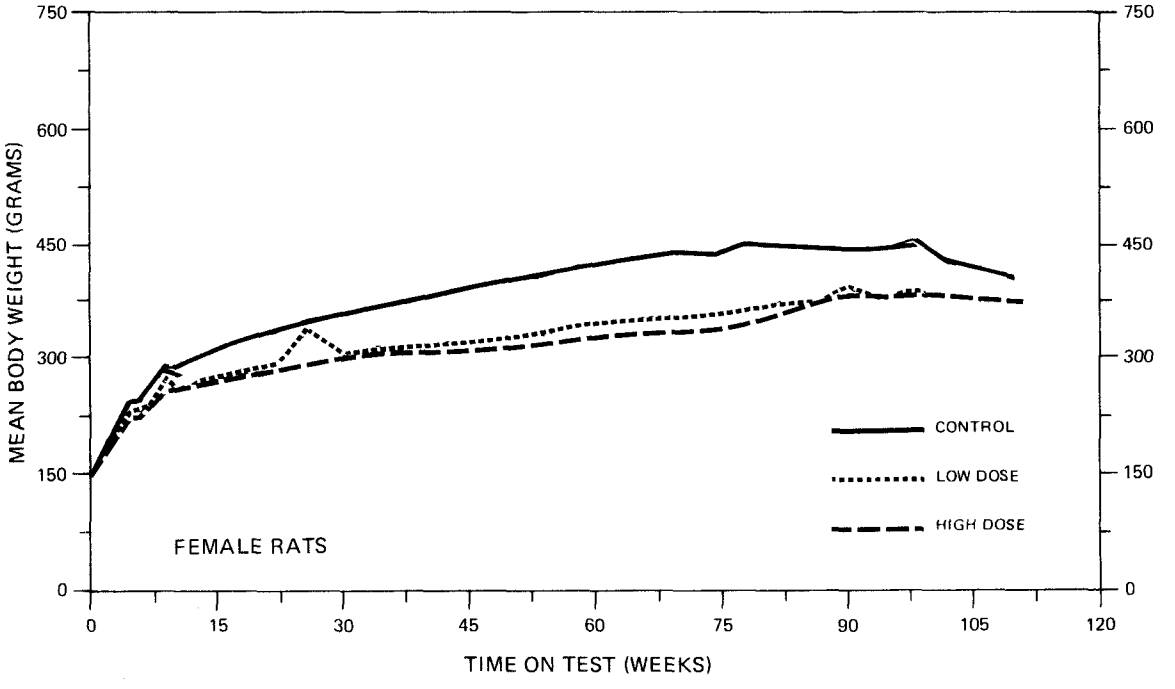
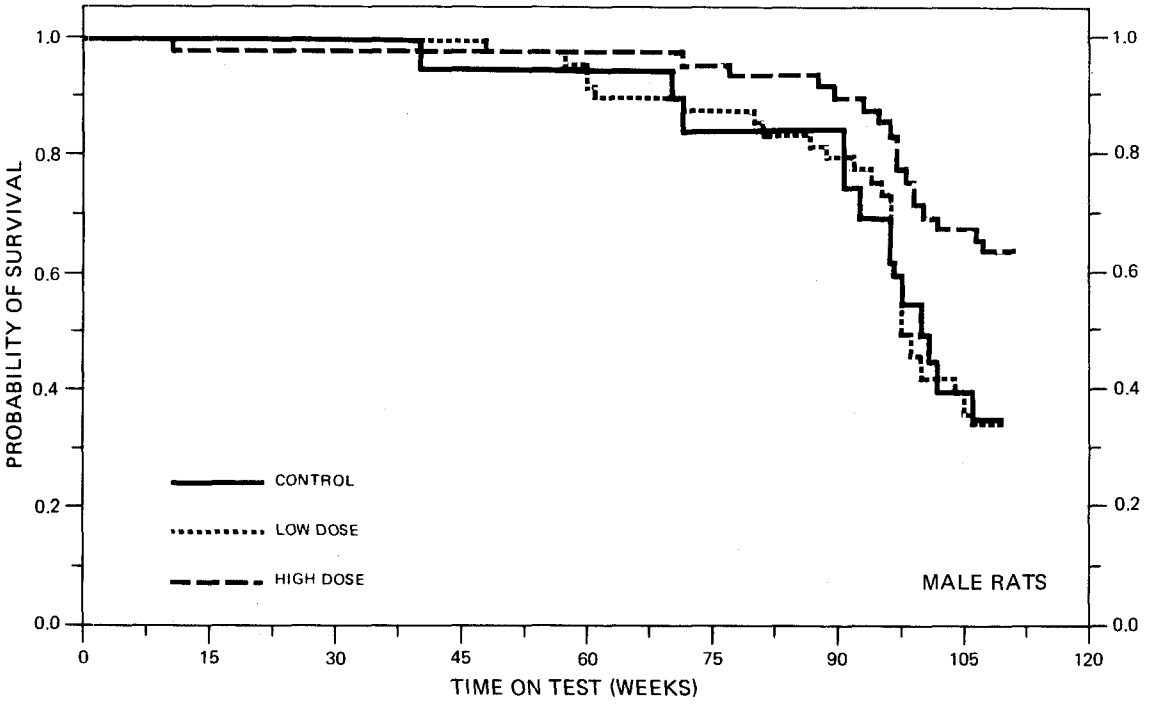


FIGURE 2
GROWTH CURVES FOR CLONITRALID CHRONIC STUDY RATS



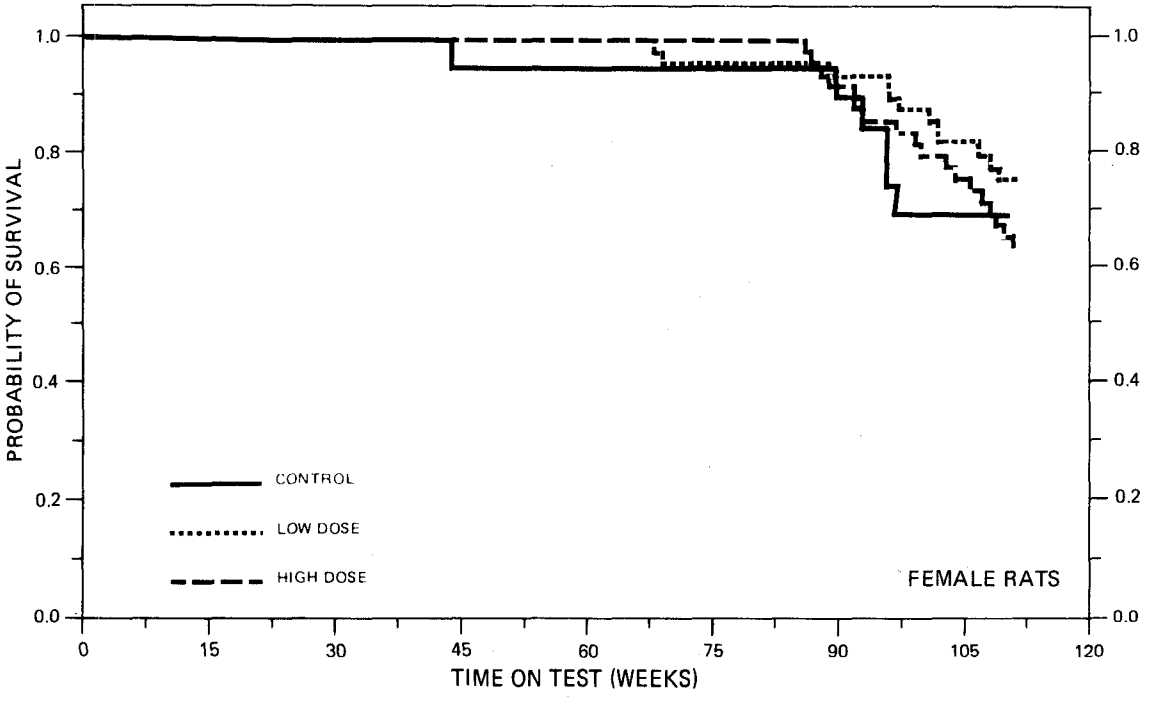


FIGURE 3
SURVIVAL COMPARISONS OF CLONITRALID CHRONIC STUDY RATS

For male rats the Tarone test for positive association between increased dosage and accelerated mortality was not significant. There were adequate numbers of male rats at risk from late-developing tumors with 92 percent (46/50) of the high dose, 80 percent (40/50) of the low dose and 85 percent (17/20) of the controls living at least 90 weeks.

For female rats the Tarone test did not show a significant association between increased dosage and accelerated mortality. With 64 percent (32/50) of the high dose, 76 percent (38/50) of the low dose, and 70 percent (14/20) of the control animals alive until the termination of the experiment, there were adequate numbers at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2).

Adenocarcinomas of the mammary gland occurred in 1/20 (5 percent) control males, 3/49 (6 percent) high dose males, 1/20 (5 percent) control females, 12/50 (24 percent) low dose females, and 11/50 (22 percent) high dose females. Microscopically, the adenocarcinomas of the mammary gland consisted of irregularly formed acini lined with anaplastic epithelial cells. A piling up of cells around the acini accompanied by papillary projections into the lumen was often observed. Some of the tumors were very cellular and were composed of tightly

packed epithelial cells in sheets or nests forming small acini. Some acini contained eosinophilic amorphous material. The neoplastic cells invaded and replaced the surrounding tissues, and lung metastasis was evident in one low dose and two high dose female rats.

Mammary fibroadenomas occurred in 1/49 (2 percent) high dose males, 4/20 (20 percent) control females, 13/50 (26 percent) low dose females, and 11/50 (22 percent) high dose females. The fibroadenomas were composed of nests and islands of mammary gland acini separated by broad bands of collagenous and fibrous connective tissue. The fibroadenomas were well-circumscribed from the surrounding tissues.

Gastric carcinomas of the glandular region of the stomach occurred in 2/45 (4 percent) high dose females. Microscopically, one of the tumors had irregular glandular acini of various sizes. The epithelial cells were supported by bands of fibrous connective tissue. In some areas, only scattered clumps of anaplastic epithelial cells were seen, typical of a scirrhous carcinoma. The neoplastic cells invaded and replaced the tunica muscularis and serosa of the stomach and metastasized to the pancreas, liver, urinary bladder, and esophagus. The other gastric carcinoma was characterized by nests and cords of poorly differentiated, large, plump cells with a scanty fibrous connective tissue stroma. Many bizarre mitotic figures were present. This tumor metastasized to the liver and lung. Nonneoplastic proliferative lesions (hyperkeratosis and acanthosis) were

observed in the stomachs of 7/41 (17 percent) low dose and 7/44 (16 percent) high dose female rats.

A greater incidence of thyroid neoplasms was observed in the treated rats than in the control groups; however, the overall incidence was not large. Both follicular-cell and C-cell tumors were observed. There was no evidence of increased numbers of preneoplastic proliferative thyroid lesions, and thyroid neoplasms have been observed with greater frequency in historical control groups. Therefore, these neoplasms are not considered to be compound-related. Pancreatic islet-cell tumors and endometrial stromal polyps were observed among treated rats, but not in associated control groups. These relatively common tumors were considered spontaneous.

Other neoplastic lesions occurred with similar frequency in the control and treated groups and were considered to have occurred naturally.

The inflammatory, degenerative, and hyperplastic lesions that occurred were similar in kind and number to those that occur spontaneously in aged Osborne-Mendel rats.

Based upon the results of this histopathologic examination clonitralid was carcinogenic in female rats, causing an increased incidence of adenocarcinomas of the mammary gland and possibly carcinomas of the glandular portion of the stomach.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH CLONITRALID[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	0/49(0.00)	4/49(0.08)
P Values[c]	P = 0.039	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.394
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	93
Circulatory System: Hemangiosarcoma[b]	2/20(0.10)	5/49(0.10)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.020	0.612
Lower Limit	---	0.188	0.078
Upper Limit	---	10.204	6.996
Weeks to First Observed Tumor	100	97	71
Pituitary: Chromophobe Adenoma[b]	5/19(0.26)	7/40(0.18)	2/33(0.06)
P Values[c]	P = 0.034(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.665	0.230
Lower Limit	---	0.217	0.025
Upper Limit	---	2.371	1.267
Weeks to First Observed Tumor	97	96	111

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/20(0.00)	4/42(0.10)	3/35(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.460	0.358
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	60	96
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	0/18(0.00)	3/41(0.07)	2/32(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.277	0.174
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	94	96
Mammary Gland: Adenocarcinoma NOS[b]	1/20(0.05)	0/49(0.00)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	1.224
Lower Limit	---	0.000	0.108
Upper Limit	---	7.624	62.958
Weeks to First Observed Tumor	91	---	88

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 14,216 or 28,433 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH CLONITRALID[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	1/20(0.05)	3/50(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.200	0.000
Lower Limit	---	0.106	0.000
Upper Limit	---	61.724	7.475
Weeks to First Observed Tumor	96	97	---
Circulatory System: Hemangiosarcoma[b]	1/20(0.05)	3/42(0.07)	2/45(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.429	0.889
Lower Limit	---	0.129	0.050
Upper Limit	---	74.895	51.294
Weeks to First Observed Tumor	110	110	111
Pituitary: Chromophobe Adenoma[b]	5/20(0.25)	7/42(0.17)	10/44(0.23)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.667	0.909
Lower Limit	---	0.215	0.337
Upper Limit	---	2.392	3.031
Weeks to First Observed Tumor	93	101	88

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	1/20(0.05)	4/41(0.10)	3/44(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.951	1.364
Lower Limit	---	0.214	0.120
Upper Limit	---	93.623	69.919
Weeks to First Observed Tumor	90	110	111
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	0/20(0.00)	1/41(0.02)	5/44(0.11)
P Values[c]	P = 0.040	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.027	0.597
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	111	103
Mammary Gland: Adenocarcinoma NOS[b]	1/20(0.05)	12/50(0.24)	11/50(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	4.800	4.400
Lower Limit	---	0.803	0.722
Upper Limit	---	200.027	184.751
Weeks to First Observed Tumor	110	69	86

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	4/20(0.20)	13/50(0.26)	11/50(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.300	1.100
Lower Limit	---	0.474	0.384
Upper Limit	---	4.977	4.321
Weeks to First Observed Tumor	90	107	104
Mammary Gland: Fibroadenoma or Adenocarcinoma NOS[b]	4/20(0.20)	21/50(0.42)	20/50(0.40)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.100	2.000
Lower Limit	---	0.846	0.799
Upper Limit	---	7.538	7.225
Weeks to First Observed Tumor	90	69	86
Uterus: Endometrial Stromal Polyp[b]	0/20(0.00)	2/41(0.05)	6/44(0.14)
P Values[c]	P = 0.036	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.150	0.758
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	96	106

TABLE 4 (CONCLUDED)

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[a]Treated groups received time-weighted average doses of 14,216 or 28,433 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or clonitralid-dosed groups and where such tumors were observed in at least 5 percent of the group.

For male rats the Cochran-Armitage test indicated a significant (P = 0.039) positive association between dosage and the incidence of fibromas of the subcutaneous tissue and a significant (P = 0.034) negative association between dosage and the incidence of pituitary chromophobe adenomas. In both cases, however, the Fisher exact tests were not significant.

Similarly, for female rats the Cochran-Armitage test indicated significant associations both between dose and the combined incidence of C-cell adenomas and C-cell carcinomas of the thyroid and between dose and the incidence of uterine endometrial stomal polyps. Once again, the Fisher exact tests were not significant.

Mammary adenocarcinomas NOS were seen in unusually high numbers in dosed rats of both sexes. In historical data collected by this laboratory for the NCI Carcinogenesis Testing Program 5/389 (1 percent) of the untreated male and 11/388 (3 percent) of the untreated female Osborne-Mendel rats had an adenocarcinoma NOS of the mammary gland. These tumors were observed in 24 percent (12/50) of the low dose and 22 percent (11/50) of the high dose females, but never in excess of 10 percent (2/20) in the 15 historical female control

groups. A life-table analysis performed for this tumor was not significant.

In females carcinomas of the stomach were observed in 2/45 (4 percent) of the high dose rats. These rare tumors were observed in none of the 350 historical control rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by clonitralid that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

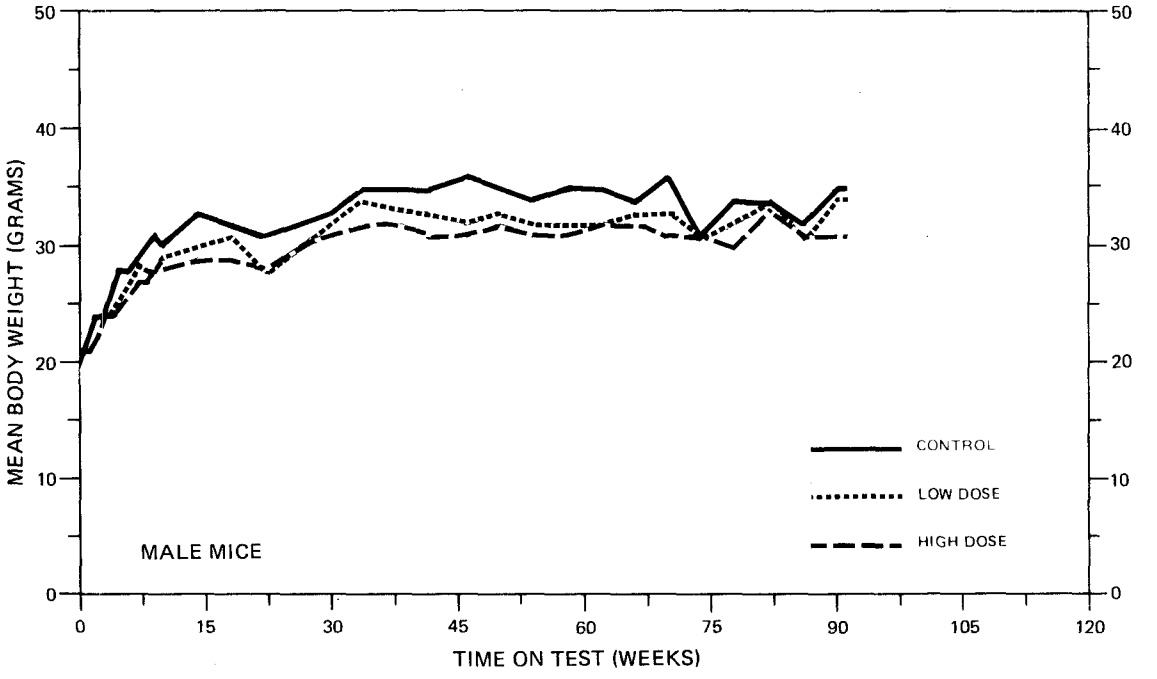
Only very slight depression in mean group body weight was observed in treated mice when compared to controls (Figure 4).

Throughout the study, appearance and behavior were generally comparable for treated and control mice except that body sores, alopecia and a hunched appearance were more frequently observed in the males. A rapidly declining survival rate was noted in treated and control males beginning in week 46 and continuing to termination of the bioassay. The low survival and clinical signs were apparently attributable to fighting in the group-housed male mice since in the females survival and a comparatively lower incidence of clinical signs were observed throughout the study. Other clinical signs commonly observed in laboratory mice were noted at a comparable rate in control and treated groups. These signs included external genital irritation, squinted or reddened eyes, rough or stained fur, and palpable nodules.

B. Survival

The estimated probabilities of survival for male and female mice in the control and clonitralid-dosed groups are shown in Figure 5.

For male mice the Tarone test for positive association between increased dosage and accelerated mortality was not significant. Five control mice drowned in week 63. There were not adequate numbers of male mice at risk from late-developing tumors, with only 32 percent



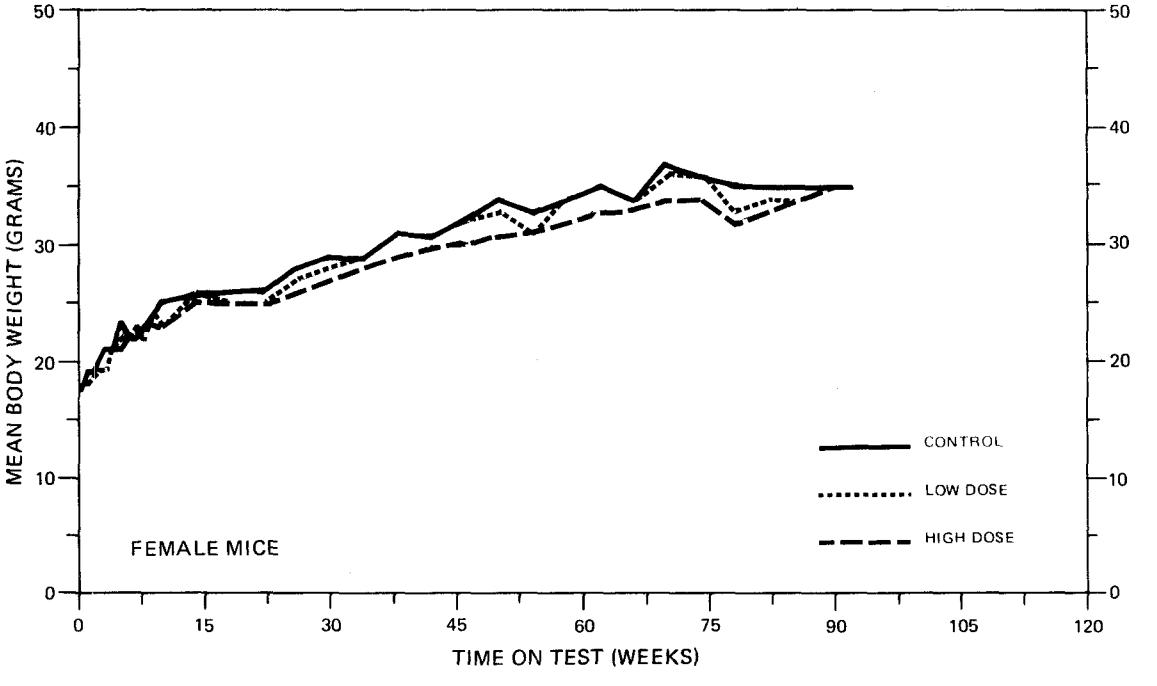
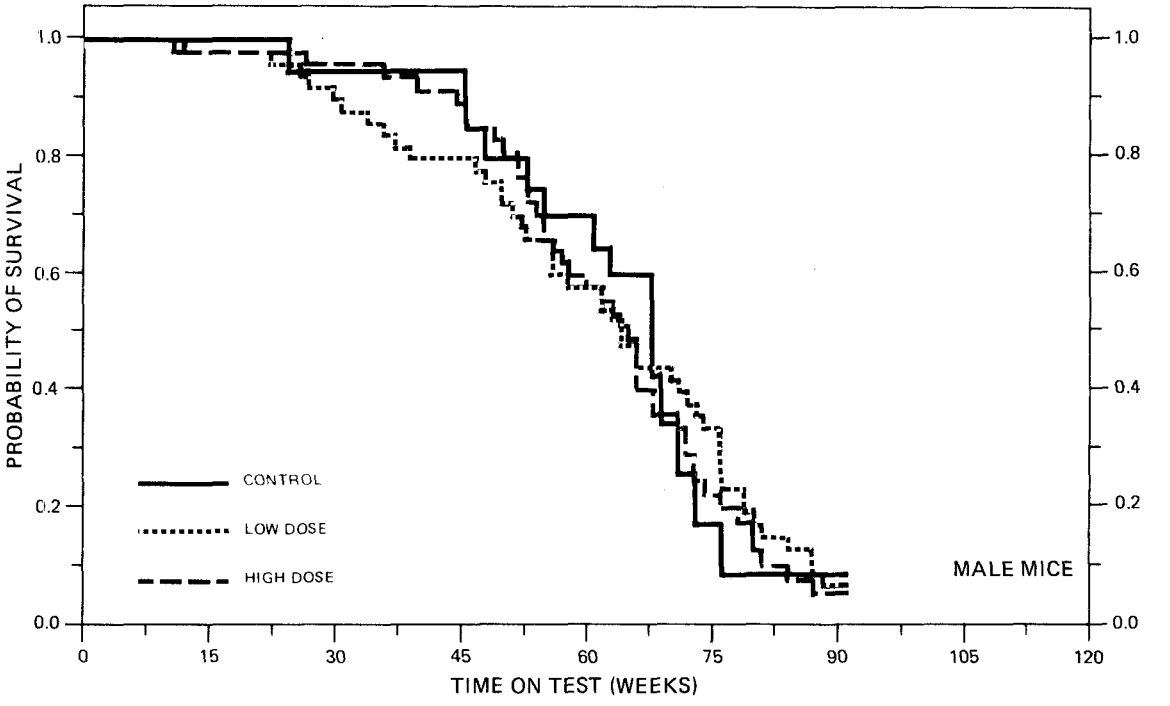


FIGURE 4
GROWTH CURVES FOR CLONITRALID CHRONIC STUDY MICE



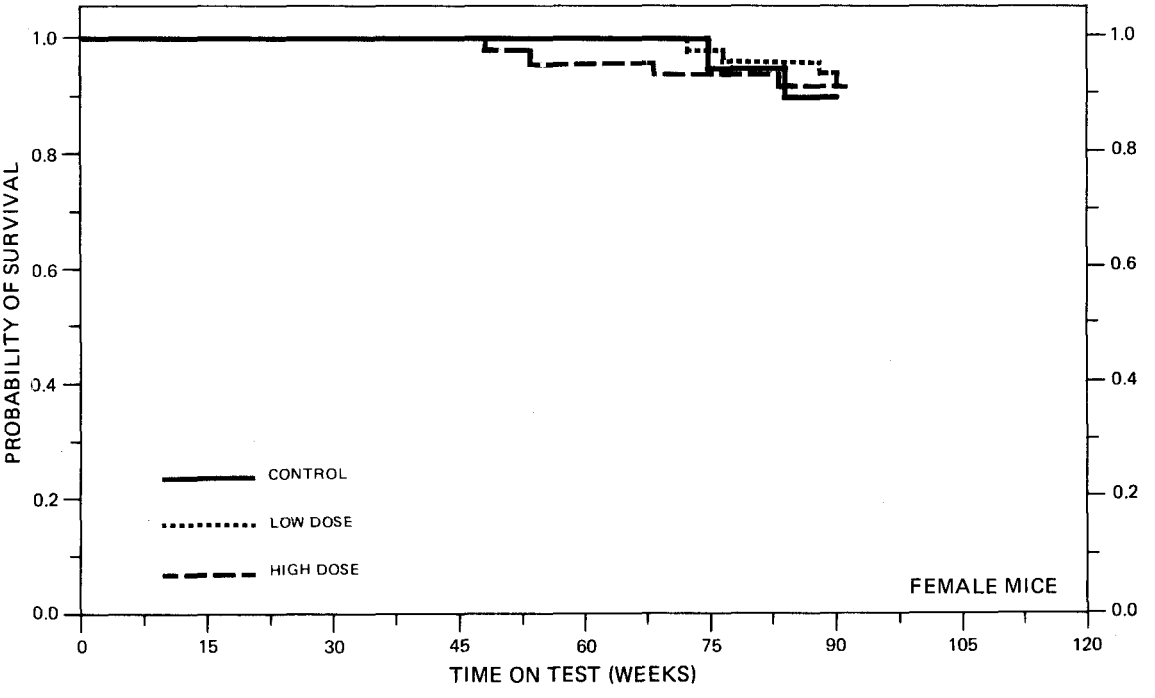


FIGURE 5
SURVIVAL COMPARISONS OF CLONITRALID CHRONIC STUDY MICE

(16/50) of the high dose, 42 percent (21/50) of the low dose, and 20 percent (4/20) of the vehicle controls alive at week 70.

For female mice the Tarone test did not show a significant association between increased dosage and accelerated mortality. With 90 percent (45/50) of the high dose, 92 percent (46/50) of the low dose, and 90 percent (18/20) of the control mice alive until the termination of the experiment, adequate numbers of female mice were at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2).

A low incidence of neoplasms was observed in both control and treated mice. These neoplasms were of the usual number and type observed in mice of this age and strain.

Other degenerative, proliferative, and inflammatory lesions observed were also of the usual number and kind observed in aged B6C3F1 mice and were essentially comparable in incidence between control and treated mice.

Based upon the results of this histopathologic examination, clonitralid was neither toxic nor carcinogenic to B6C3F1 mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH CLONITRALID[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	0/16(0.00)	2/43(0.05)	3/43(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.116	0.237
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	62	68

[a]Treated groups received time-weighted average doses of 274 or 549 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH CLONITRALID[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	2/20(0.10)	0/49(0.00)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.213
Lower Limit	---	0.000	0.004
Upper Limit	---	1.372	3.909
Weeks to First Observed Tumor	91	---	92
Hematopoietic System: Malignant Lymphoma[b]	4/20(0.20)	4/49(0.08)	1/47(0.02)
P Values[c]	P = 0.014(N)	N.S.	P = 0.025(N)
Relative Risk (Control)[d]	---	0.408	0.106
Lower Limit	---	0.086	0.002
Upper Limit	---	2.022	1.003
Weeks to First Observed Tumor	85	89	92

[a]Treated groups received time-weighted average doses of 274 or 549 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or clonitralid-dosed groups and where such tumors were observed in at least 5 percent of the group.

In female mice the Cochran-Armitage test indicated a significant ($P = 0.014$) negative association between dosage and the incidence of malignant lymphomas. The Fisher exact test comparing the incidence of these tumors in the high dose treated group with that in the control mice had a probability level of $P = 0.025$, a marginal result which was not significant under the Bonferroni criterion.

None of the statistical tests for any site in mice of either sex indicated a significant positive association between the administration of clonitralid and tumor incidence. Thus, at the dose levels used in this experiment there was no convincing evidence that clonitralid was a carcinogen in mice. It must be noted, however, that poor survival precluded meaningful statistical analyses of the incidence of late-developing tumors in male mice.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In all of the intervals shown in Tables 5 and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that all of the confidence intervals have an upper limit greater than one,

indicating the theoretical possibility of tumor induction in mice by clonitralid that could not be established under the conditions of this test.

V. DISCUSSION

Adequate numbers of male rats, female rats, and female mice survived long enough to be at risk from late-developing tumors. Because of inadequate survival among male mice, however, results obtained from observation of the male mouse groups cannot be considered conclusive.

Although some neoplasms were observed at higher incidences in dosed rats than control rats, none of these increased incidences were statistically significant. The incidence of subcutaneous fibromas in male rats, the combined incidence of C-cell adenomas and C-cell carcinomas of the thyroid in female rats, and the incidence of endometrial stromal polyps in female rats each were found to have a significant positive association with clonitralid dosage. The Fisher exact test, however, did not indicate that the incidence in a dosed group was significantly greater than the incidence in the respective control group in any of these cases.

The incidences of mammary adenocarcinomas in dosed female rats, although not significantly higher than the incidences observed in control female rats, were greater than or equal to 22 percent, while the highest spontaneous incidence of this lesion observed in 15 control groups at this laboratory was only 10 percent with a mean incidence of 2.6 percent. The observation of mammary adenocarcinomas in the dosed males (3/49) supports the findings in the females. The occurrence in high dose female rats (2/45) of carcinomas of the glandular portion of the stomach with metastases to other sites was not

statistically significant. This incidence, however, is much greater than the historical incidence (i.e., 0/350) observed in control female rats maintained at Hazleton Laboratories during the NCI Carcinogenesis Testing Program and suggests an association between administration of clonitralid and the development of these tumors.

No significantly increased tumor incidences were observed among mice treated with clonitralid.

Under the conditions of this bioassay, there was no convincing evidence that clonitralid was carcinogenic to Osborne-Mendel rats or to female B6C3F1 mice. Poor survival of male mice did not permit an evaluation of carcinogenicity in these animals.

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Review of the Bioassay of Clonitralid* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Clonitralid for carcinogenicity.

Although the carcinogenicity of the compound was not established under the conditions of test, the reviewer said that the study should not be considered "definitive." He pointed out the finding of mammary adenocarcinomas in both the treated and control female rats, as well as in treated male rats. The reviewer concluded that the evidence was insufficient to declare that Clonitralid was carcinogenic but that it raised "concern that the study may not have been definitive." The reviewer's conclusion was accepted without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH CLONITRALID

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH CLONITRALID

	CONTROL(VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	43	36
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(49)	(49)
FIBROMA			4 (8%)
FIBROSARCOMA		2 (4%)	
LIPOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(43)	(36)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	1 (2%)
#SPLEEN	(18)	(43)	(35)
HEMANGIOSARCOMA	2 (11%)	3 (7%)	3 (9%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#PANCREAS	(18)	(41)	(32)
HEMANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(43)	(35)
MIXED TUMOR, MALIGNANT		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL(VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(40)	(33)
CHROMOPHOBE ADENOMA	5 (26%)	7 (18%)	2 (6%)
#ADRENAL	(19)	(43)	(36)
CORTICAL CARCINOMA	1 (5%)	1 (2%)	2 (6%)
PHEOCHROMOCYTOMA		1 (2%)	1 (3%)
#THYROID	(20)	(42)	(35)
FOLLICULAR-CELL ADENOMA		2 (5%)	3 (9%)
FOLLICULAR-CELL CARCINOMA		2 (5%)	
C-CELL ADENOMA		1 (2%)	3 (9%)
#PANCREATIC ISLETS	(18)	(41)	(32)
ISLET-CELL ADENOMA		3 (7%)	1 (3%)
ISLET-CELL CARCINOMA			1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(49)
ADENOCARCINOMA, NOS	1 (5%)		3 (6%)
FIBROADENOMA			1 (2%)
*PREPUTIAL GLAND	(20)	(49)	(49)
ADENOCARCINOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(42)	(36)
OLIGODENDROGLIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*TUNICA VAGINALIS	(20)	(49)	(49)
MESOTHELIOMA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONCLUDED)

	CONTROL (VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
ALL OTHER SYSTEMS			
THORACIC CAVITY			
LIPOSARCOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	13	33	17
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	7	17	32
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	20	20
TOTAL PRIMARY TUMORS	11	30	26
TOTAL ANIMALS WITH BENIGN TUMORS	5	11	13
TOTAL BENIGN TUMORS	5	15	15
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	12	10
TOTAL MALIGNANT TUMORS	6	14	11
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH CLONITRALID

	CONTROL(VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	42	45
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
FIBROSARCOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA	1 (5%)	3 (6%)	
FIBROSARCOMA		2 (4%)	
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(42)	(45)
CARCINOMA, NOS, METASTATIC			2 (4%)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	2 (4%)
FIBROSARCOMA, METASTATIC		1 (2%)	1 (2%)
HEMANGIOSARCOMA	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
GRANULOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(20)	(41)	(45)
CARCINOMA, NOS, METASTATIC			1 (2%)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
#CERVICAL LYMPH NODE	(20)	(39)	(43)
CARCINOMA, NOS, METASTATIC			1 (2%)
#MESENTERIC L. NODE	(20)	(39)	(43)
CARCINOMA, NOS, METASTATIC			1 (2%)
HEMANGIOSARCOMA		2 (5%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(42)	(45)
CARCINOMA, NOS, METASTATIC			1 (2%)
NEOPLASTIC NODULE		1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)
CORTICAL CARCINOMA, METASTATIC		1 (2%)	
#PANCREAS	(19)	(40)	(45)
CARCINOMA, NOS, METASTATIC			2 (4%)
#ESOPHAGUS	(20)	(41)	(44)
CARCINOMA, NOS, METASTATIC			1 (2%)
#STOMACH	(20)	(42)	(45)
CARCINOMA, NOS			2 (4%)
#SMALL INTESTINE	(19)	(41)	(43)
CARCINOMA, NOS, METASTATIC			1 (2%)
#LARGE INTESTINE	(20)	(42)	(45)
CARCINOMA, NOS, METASTATIC			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(42)	(45)
CARCINOMA, NOS, METASTATIC			1 (2%)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
MIXED TUMOR, MALIGNANT		2 (5%)	
HAMARTOMA +	1 (5%)	1 (2%)	
#URINARY BLADDER	(19)	(38)	(45)
CARCINOMA, NOS, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(42)	(44)
CHROMOPHOBE ADENOMA	5 (25%)	7 (17%)	10 (23%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
#ADRENAL	(20)	(42)	(44)
CARCINOMA, NOS, METASTATIC			1 (2%)
CORTICAL ADENOMA		2 (5%)	
CORTICAL CARCINOMA		2 (5%)	1 (2%)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(20)	(41)	(44)
FOLLICULAR-CELL ADENOMA	1 (5%)	2 (5%)	1 (2%)
FOLLICULAR-CELL CARCINOMA		2 (5%)	2 (5%)
C-CELL ADENOMA		1 (2%)	3 (7%)
C-CELL CARCINOMA			2 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)	12 (24%)	11 (22%)
FIBROADENOMA	4 (20%)	13 (26%)	11 (22%)
*PREPUTIAL GLAND	(20)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
#UTERUS	(20)	(41)	(44)
CARCINOMA, NOS, METASTATIC			1 (2%)
SQUAMOUS CELL CARCINOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		2 (5%)	6 (14%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)
HEMANGIOSARCOMA			1 (2%)
#OVARY	(19)	(41)	(43)
CARCINOMA, NOS, METASTATIC			1 (2%)
GRANULOSA-CELL TUMOR	1 (5%)	1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONCLUDED)

	CONTROL(VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
FIBROSARCOMA	1 (5%)		
*MESENTERY	(20)	(50)	(50)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
ALL OTHER SYSTEMS			
DIAPHRAGM			
CARCINOMA, NOS, METASTATIC			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	12	17
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	38	32
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	33	37
TOTAL PRIMARY TUMORS	16	59	61
TOTAL ANIMALS WITH BENIGN TUMORS	10	22	24
TOTAL BENIGN TUMORS	12	31	33
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	24	23
TOTAL MALIGNANT TUMORS	3	26	27
TOTAL ANIMALS WITH SECONDARY TUMORS#		3	5
TOTAL SECONDARY TUMORS		3	21
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	2	1
TOTAL UNCERTAIN TUMORS	1	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH CLONITRALID

TABLE B1

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH CLONITRALID

	CONTROL (VEH) 02-M052	LOW DOSE 02-M053	HIGH DOSE 02-M054
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	16	43	43
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	16	43	43
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(16)	(43)	(43)
FIBROSARCOMA		2 (5%)	3 (7%)
RESPIRATORY SYSTEM			
#LUNG	(16)	(43)	(43)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(16)	(43)	(43)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)
#KIDNEY	(16)	(43)	(43)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (6%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(16)	(43)	(43)
HEPATOCELLULAR CARCINOMA		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL(VEH) 02-M052	LOW DOSE 02-M053	HIGH DOSE 02-M054
REPRODUCTIVE SYSTEM			
#TESTIS	(16)	(42)	(43)
INTERSTITIAL-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	19	46	43
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			2
TERMINAL SACRIFICE	1	3	2
ANIMAL MISSING		1	3

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONCLUDED)

	CONTROL(VEH) 02-M052	LOW DOSE 02-M053	HIGH DOSE 02-M054
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	1	5	5
TOTAL PRIMARY TUMORS	1	5	5
TOTAL ANIMALS WITH BENIGN TUMORS		1	1
TOTAL BENIGN TUMORS		1	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	4	4
TOTAL MALIGNANT TUMORS	1	4	4
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH CLONITRALID

	CONTROL (VEH) 02-F052	LOW DOSE 02-F055	HIGH DOSE 02-F056
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(47)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (20%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		3 (6%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
NONE			
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL(VEH) 02-F052	LOW DOSE 02-F055	HIGH DOSE 02-F056
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(47)
ADENOCARCINOMA, NOS	1 (5%)		1 (2%)
#UTERUS	(20)	(49)	(46)
ENDOMETRIAL STROMAL POLYP		1 (2%)	1 (2%)
#OVARY	(18)	(48)	(45)
CYSTADENOMA, NOS	1 (6%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(20)	(49)	(47)
ADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	4	4
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	46	45
ANIMAL MISSING			1

@ INCLUDES AUTOLYZED ANIMALS

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONCLUDED)

	CONTROL(VEH) 02-F052	LOW DOSE 02-F055	HIGH DOSE 02-F056
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	9	5	5
TOTAL PRIMARY TUMORS	9	5	5
TOTAL ANIMALS WITH BENIGN TUMORS	3	1	3
TOTAL BENIGN TUMORS	3	1	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	4	2
TOTAL MALIGNANT TUMORS	6	4	2
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH CLONITRALID

TABLE C1

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH CLONITRALID

	CONTROL(VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	43	36
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(49)
EPIDERMAL INCLUSION CYST			1 (2%)
*SUBCUT TISSUE	(20)	(49)	(49)
ULCER, NOS		1 (2%)	
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(20)	(49)	(49)
INFLAMMATION, NOS			2 (4%)
#LUNG/BRONCHUS	(20)	(43)	(36)
ABSCESS, NOS		8 (19%)	
#LUNG	(20)	(43)	(36)
MINERALIZATION		1 (2%)	
ATELECTASIS			1 (3%)
CONGESTION, NOS	5 (25%)	17 (40%)	
EDEMA, NOS		2 (5%)	
INFLAMMATION, NECROTIZING		1 (2%)	
PNEUMONIA, CHRONIC MURINE	18 (90%)	40 (93%)	24 (67%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(43)	(35)
INFLAMMATION, NOS			1 (3%)
PERIARTERITIS	1 (6%)		
HEMATOPOIESIS		3 (7%)	1 (3%)
#MESENTERIC L. NODE	(18)	(36)	(33)
INFLAMMATION, NOS			1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
CIRCULATORY SYSTEM			
#HEART	(20)	(43)	(36)
DILATATION, NOS		1 (2%)	
FIBROSIS			1 (3%)
PERIARTERITIS		1 (2%)	
CALCIUM DEPOSIT	1 (5%)		
#MYOCARDIUM	(20)	(43)	(36)
MINERALIZATION			1 (3%)
INFLAMMATION, NOS	3 (15%)		2 (6%)
INFLAMMATION, FOCAL	3 (15%)		
INFLAMMATION, DIFFUSE	1 (5%)		
INFLAMMATION, INTERSTITIAL	1 (5%)		
FIBROSIS		4 (9%)	1 (3%)
FIBROSIS, DIFFUSE		2 (5%)	
DEGENERATION, NOS			6 (17%)
CALCIFICATION, NOS		1 (2%)	
#ENDOCARDIUM	(20)	(43)	(36)
INFLAMMATION, NOS			1 (3%)
FIBROSIS			1 (3%)
*AORTA	(20)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
ARTERIOSCLEROSIS, NOS			2 (4%)
MEDIAL CALCIFICATION		2 (4%)	
CALCIUM DEPOSIT			1 (2%)
CALCIFICATION, NOS		1 (2%)	
*CORONARY ARTERY	(20)	(49)	(49)
MINERALIZATION		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(11)	(22)	(28)
HYPERPLASIA, INTRADUCTAL	1 (9%)		
#LIVER	(20)	(43)	(36)
CONGESTION, NOS	4 (20%)	12 (28%)	
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS	1 (5%)		
METAMORPHOSIS FATTY	2 (10%)	7 (16%)	1 (3%)
FOCAL CELLULAR CHANGE		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
HYPERPLASTIC NODULE	1 (5%)		
HYPERPLASIA, NOS		1 (2%)	2 (6%)
#LIVER/CENTRILOBULAR	(20)	(43)	(36)
DEGENERATION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY		2 (5%)	
#LIVER/HEPATOCYTES	(20)	(43)	(36)
INFLAMMATION, NOS		2 (5%)	
INFLAMMATION, DIFFUSE		1 (2%)	
HYPERPLASIA, NOS	1 (5%)	1 (2%)	
*BILE DUCT	(20)	(49)	(49)
INFLAMMATION, NOS	5 (25%)	3 (6%)	
HYPERPLASIA, NOS	6 (30%)	19 (39%)	6 (12%)
#PANCREAS	(18)	(41)	(32)
THROMBOSIS, NOS			1 (3%)
PERIARTERITIS	2 (11%)	4 (10%)	
ATROPHY, NOS	2 (11%)	3 (7%)	2 (6%)
#STOMACH	(20)	(43)	(35)
MINERALIZATION	2 (10%)	4 (9%)	
HEMORRHAGE		2 (5%)	
ULCER, NOS	3 (15%)	3 (7%)	
ULCER, FOCAL	1 (5%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (3%)
CALCIUM DEPOSIT			3 (9%)
ACANTHOSIS	1 (5%)		
#GASTRIC MUCOSA	(20)	(43)	(35)
MINERALIZATION		1 (2%)	
#LARGE INTESTINE	(18)	(43)	(34)
NEMATODIASIS		1 (2%)	2 (6%)
URINARY SYSTEM			
#KIDNEY	(20)	(43)	(35)
MINERALIZATION	1 (5%)	1 (2%)	
HYDRONEPHROSIS			1 (3%)
CONGESTION, NOS	5 (25%)	18 (42%)	
INFLAMMATION, CHRONIC	17 (85%)	34 (79%)	22 (63%)
#KIDNEY/CORTEX	(20)	(43)	(35)
CYST, NOS	3 (15%)	6 (14%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
#KIDNEY/PELVIS	(20)	(43)	(35)
INFLAMMATION, NOS		2 (5%)	
#URINARY BLADDER	(18)	(41)	(34)
INFLAMMATION, NOS	1 (6%)	2 (5%)	2 (6%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(40)	(33)
CYST, NOS		2 (5%)	
HYPERPLASIA, CHROMOPHOBE-CELL	2 (11%)	2 (5%)	
#ADRENAL	(19)	(43)	(36)
CONGESTION, NOS	2 (11%)		
ANGIECTASIS	2 (11%)	3 (7%)	3 (8%)
#ADRENAL CORTEX	(19)	(43)	(36)
DEGENERATION, NOS	7 (37%)	10 (23%)	3 (8%)
#THYROID	(20)	(42)	(35)
COLLOID CYST	1 (5%)	1 (2%)	
HYPERPLASIA, C-CELL	2 (10%)	1 (2%)	1 (3%)
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)	1 (2%)	1 (3%)
#PARATHYROID	(1)	(4)	(3)
HYPERPLASIA, NOS	1 (100%)	4 (100%)	3 (100%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(13)	(30)	(26)
INFLAMMATION, NOS	2 (15%)	4 (13%)	2 (8%)
*SEMINAL VESICLE	(20)	(49)	(49)
INFLAMMATION, NOS		1 (2%)	
#TESTIS	(20)	(43)	(36)
PERIARTERITIS	1 (5%)		
ATROPHY, NOS	5 (25%)	16 (37%)	4 (11%)
ASPERMATOGENESIS	2 (10%)	9 (21%)	2 (6%)
HYPOSPERMATOGENESIS	4 (20%)	7 (16%)	1 (3%)
*EPIDIDYMIS	(20)	(49)	(49)
NECROSIS, FAT			3 (6%)
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONCLUDED)

	CONTROL (VEH) 01-M046	LOW DOSE 01-M047	HIGH DOSE 01-M048
SPECIAL SENSE ORGANS			
*EYE	(20)	(49)	(49)
INFLAMMATION, NOS		1 (2%)	
*EYE/CORNEA	(20)	(49)	(49)
INFLAMMATION, NOS		2 (4%)	
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(49)	(49)
MINERALIZATION	1 (5%)		
INFLAMMATION, NOS	1 (5%)	1 (2%)	
FIBROSIS		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(49)
INFLAMMATION, CHRONIC	1 (5%)		
PERIARTERITIS		1 (2%)	
NECROSIS, FAT	1 (5%)		1 (2%)
*PERITONEUM	(20)	(49)	(49)
INFLAMMATION, NOS			2 (4%)
*PERICARDIUM	(20)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*MESENTERY	(20)	(49)	(49)
PERIARTERITIS	1 (5%)	6 (12%)	5 (10%)
NECROSIS, FAT		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED		6	13
AUTOLYSIS/NO NECROPSY		1	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH CLONITRALID

	CONTROL (VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	42	45
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
ABSCESS, NOS			2 (4%)
ABSCESS, CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LUNG/BRONCHUS	(20)	(42)	(45)
ABSCESS, NOS	2 (10%)	2 (5%)	
#LUNG	(20)	(42)	(45)
CONGESTION, NOS	3 (15%)	21 (50%)	1 (2%)
ABSCESS, NOS	1 (5%)		
PNEUMONIA, CHRONIC MURINE	18 (90%)	41 (98%)	29 (64%)
#ALVEOLAR WALL	(20)	(42)	(45)
EPITHELIALIZATION	1 (5%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(41)	(43)
METAMORPHOSIS FATTY			1 (2%)
#SPLEEN	(20)	(41)	(45)
HEMATOPOIESIS	2 (10%)	7 (17%)	10 (22%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(42)	(44)
INFLAMMATION, NOS	1 (5%)	1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL(VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
INFLAMMATION, DIFFUSE	1 (5%)		
FIBROSIS		4 (10%)	
FIBROSIS, DIFFUSE		1 (2%)	
DEGENERATION, NOS			3 (7%)
#ENDOCARDIUM	(20)	(42)	(44)
INFLAMMATION, NOS			1 (2%)
FIBROSIS		2 (5%)	
HYPERPLASIA, NOS			1 (2%)
*AORTA	(20)	(50)	(50)
ARTERIOSCLEROSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(14)	(34)	(38)
INFLAMMATION, CHRONIC	1 (7%)		
ATROPHY, NOS			1 (3%)
#LIVER	(20)	(42)	(45)
CONGESTION, NOS	3 (15%)	4 (10%)	
NECROSIS, NOS	1 (5%)		
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	2 (10%)	5 (12%)	1 (2%)
FOCAL CELLULAR CHANGE		3 (7%)	
HYPERPLASIA, FOCAL	1 (5%)		
HEMATOPOIESIS		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(42)	(45)
METAMORPHOSIS FATTY	1 (5%)		
#LIVER/HEPATOCYTES	(20)	(42)	(45)
DEGENERATION, NOS		1 (2%)	
NECROSIS, NOS	1 (5%)		
FOCAL CELLULAR CHANGE	1 (5%)		
HYPERPLASIA, NOS	3 (15%)		
*BILE DUCT	(20)	(50)	(50)
DILATATION, NOS		1 (2%)	
CONGESTION, NOS		1 (2%)	
INFLAMMATION, NOS	3 (15%)	12 (24%)	2 (4%)
HYPERPLASIA, NOS	4 (20%)	17 (34%)	7 (14%)
#PANCREAS	(19)	(40)	(45)
PERIARTERITIS		1 (3%)	3 (7%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
CALCIUM DEPOSIT			1 (2%)
ATROPHY, NOS			1 (2%)
#ESOPHAGUS	(20)	(41)	(44)
ULCER, NOS	1 (5%)		
#STOMACH	(20)	(42)	(45)
HEMORRHAGE		2 (5%)	
INFLAMMATION, NOS	1 (5%)		
ULCER, NOS		3 (7%)	1 (2%)
ULCER, FOCAL	2 (10%)	1 (2%)	1 (2%)
CALCIUM DEPOSIT			1 (2%)
HYPERKERATOSIS		3 (7%)	4 (9%)
ACANTHOSIS		4 (10%)	3 (7%)
#LARGE INTESTINE	(20)	(42)	(45)
NEMATODIASIS		4 (10%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(42)	(45)
MINERALIZATION	1 (5%)		
HYDRONEPHROSIS			1 (2%)
CONGESTION, NOS	3 (15%)	15 (36%)	
INFLAMMATION, CHRONIC	13 (65%)	19 (45%)	14 (31%)
#KIDNEY/CORTEX	(20)	(42)	(45)
CYST, NOS		3 (7%)	
#KIDNEY/PELVIS	(20)	(42)	(45)
CALCULUS, NOS		1 (2%)	
INFLAMMATION, NOS		4 (10%)	
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(42)	(44)
CYST, NOS	1 (5%)	2 (5%)	
HEMORRHAGIC CYST		1 (2%)	4 (9%)
HYPERPLASIA, CHROMOPHOBE-CELL	2 (10%)	3 (7%)	
#ADRENAL	(20)	(42)	(44)
CONGESTION, NOS	1 (5%)		
DEGENERATION, NOS		3 (7%)	1 (2%)
ATROPHY, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
ANGIECTASIS	9 (45%)	14 (33%)	10 (23%)
#ADRENAL CORTEX	(20)	(42)	(44)
DEGENERATION, NOS	12 (60%)	18 (43%)	8 (18%)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (5%)		
#THYROID	(20)	(41)	(44)
HYPERPLASIA, C-CELL	2 (10%)	3 (7%)	
HYPERPLASIA, FOLLICULAR-CELL			2 (5%)
#PARATHYROID			(1)
HYPERPLASIA, NOS			1 (100%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
GALACTOCELE	1 (5%)		
NECROSIS, NOS		1 (2%)	
#UTERUS	(20)	(41)	(44)
HYDROMETRA	3 (15%)	2 (5%)	3 (7%)
THROMBOSIS, NOS			1 (2%)
HEMORRHAGIC CYST	1 (5%)		
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (5%)		
#UTERUS/ENDOMETRIUM	(20)	(41)	(44)
INFLAMMATION, NOS	1 (5%)	2 (5%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS	1 (5%)		1 (2%)
HYPERPLASIA, CYSTIC	1 (5%)	10 (24%)	4 (9%)
#OVARY/OVIDUCT	(20)	(41)	(44)
INFLAMMATION, SUPPURATIVE	1 (5%)		
#OVARY	(19)	(41)	(43)
CYST, NOS	1 (5%)	1 (2%)	3 (7%)
FOLLICULAR CYST, NOS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F046	LOW DOSE 01-F047	HIGH DOSE 01-F048
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
NECROSIS, FAT	1 (5%)		
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS		1 (2%)	3 (6%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED		8	5

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH CLONITRALID

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH CLONITRALID

	CONTROL(VEH) 02-M052	LOW DOSE 02-M053	HIGH DOSE 02-M054
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	3
ANIMALS NECROPSIED	16	43	43
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	16	43	43
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(16)	(43)	(43)
PNEUMONIA, CHRONIC MURINE	1 (6%)	2 (5%)	1 (2%)
AMYLOIDOSIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(16)	(42)	(42)
AMYLOIDOSIS	9 (56%)	26 (62%)	34 (81%)
#MESENTERIC L. NODE	(13)	(33)	(39)
INFLAMMATION, NOS		1 (3%)	
ANGIECTASIS	1 (8%)	2 (6%)	
CIRCULATORY SYSTEM			
#HEART	(16)	(43)	(43)
THROMBUS, ORGANIZED		1 (2%)	3 (7%)
CALCIUM DEPOSIT			1 (2%)
#MYOCARDIUM	(16)	(43)	(43)
INFLAMMATION, NOS			2 (5%)
#ENDOCARDIUM	(16)	(43)	(43)
INFLAMMATION, NOS		1 (2%)	2 (5%)
DIGESTIVE SYSTEM			
#LIVER	(16)	(43)	(43)
AMYLOIDOSIS	2 (13%)	8 (19%)	3 (7%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M052	LOW DOSE 02-M053	HIGH DOSE 02-M054
#STOMACH	(16)	(41)	(43)
ULCER, FOCAL		1 (2%)	
CALCIUM DEPOSIT	1 (6%)		
HYPERKERATOSIS	2 (13%)		
ACANTHOSIS	2 (13%)		
#COLON	(16)	(41)	(43)
NEMATODIASIS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(16)	(43)	(43)
PYELONEPHRITIS, NOS	1 (6%)	1 (2%)	3 (7%)
INFLAMMATION, CHRONIC	12 (75%)	30 (70%)	33 (77%)
AMYLOIDOSIS	1 (6%)	9 (21%)	7 (16%)
#URINARY BLADDER	(16)	(42)	(43)
INFLAMMATION, NOS	3 (19%)		1 (2%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#PROSTATE	(14)	(37)	(41)
INFLAMMATION, NOS	3 (21%)		2 (5%)
*SEMINAL VESICLE	(16)	(43)	(43)
INFLAMMATION, NOS			1 (2%)
GRANULOMA, SPERMATIC			1 (2%)
#TESTIS	(16)	(42)	(43)
CALCIFICATION, NOS			1 (2%)
ATROPHY, NOS			3 (7%)
*EPIDIDYMIS	(16)	(43)	(43)
INFLAMMATION, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(15)	(43)	(43)
INFLAMMATION, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 02-M052	LOW DOSE 02-M053	HIGH DOSE 02-M054
#BRAIN	(15)	(43)	(43)
INFLAMMATION, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*OPTIC NERVE HEAD	(16)	(43)	(43)
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	9	4
ANIMAL MISSING/NO NECROPSY		1	3
AUTOLYSIS/NO NECROPSY	4	6	4

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH CLONITRALID

	CONTROL (VEH) 02-F052	LOW DOSE 02-F055	HIGH DOSE 02-F056
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	49	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	49	47
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(47)
PNEUMONIA, CHRONIC MURINE	1 (5%)	5 (10%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(47)
ANGIECTASIS			1 (2%)
HEMATOPOIESIS		2 (4%)	1 (2%)
#CERVICAL LYMPH NODE	(20)	(48)	(43)
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(20)	(48)	(43)
HYPERPLASIA, NOS	1 (5%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(49)	(47)
INFLAMMATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(47)
INFLAMMATION, NOS		2 (4%)	
#PANCREAS	(20)	(49)	(47)
INFLAMMATION, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F052	LOW DOSE 02-F055	HIGH DOSE 02-F056
#STOMACH	(20)	(49)	(47)
INFLAMMATION, NOS			1 (2%)
HYPERKERATOSIS	1 (5%)		
ACANTHOSIS	1 (5%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(38)	(36)
ANGIECTASIS	1 (6%)	1 (3%)	
#ADRENAL	(20)	(48)	(47)
ANGIECTASIS	1 (5%)		
#ADRENAL CORTEX	(20)	(48)	(47)
DEGENERATION, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(49)	(46)
HYDROMETRA		4 (8%)	5 (11%)
INFLAMMATION, NOS	4 (20%)	10 (20%)	5 (11%)
#UTERUS/ENDOMETRIUM	(20)	(49)	(46)
INFLAMMATION, NOS	1 (5%)		
HYPERPLASIA, CYSTIC	4 (20%)	11 (22%)	10 (22%)
#OVARY/OVIDUCT	(20)	(49)	(46)
INFLAMMATION, NOS		1 (2%)	1 (2%)
#OVARY	(18)	(48)	(45)
FOLLICULAR CYST, NOS	1 (6%)	4 (8%)	10 (22%)
PAROVARIAN CYST	2 (11%)	5 (10%)	1 (2%)
INFLAMMATION, NOS	3 (17%)	10 (21%)	10 (22%)
INFLAMMATION, SUPPURATIVE	1 (6%)		
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONCLUDED)

	CONTROL(VEH) 02-F052	LOW DOSE 02-F055	HIGH DOSE 02-F056
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(20)	(49)	(47)
ULCER, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	12	13
ANIMAL MISSING/NO NECROPSY			1
AUTOLYSIS/NO NECROPSY		1	2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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