資料６

出典　National Cancer Institute, TR-97. Bioassay of Titanium Dioxide for Possible Carcinogenicity. (1979)

二酸化チタン発がん性試験

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要約

Fisher 344 系ラット及び B6C3F1 系マウスに二酸化チタンを投与して、　その発がん性の可能性について生物検定を実施した。

雌雄各 50 匹のラット及び雌雄各 50 匹のマウスに、25,000ppm あるいは 50,000ppm の濃度のどちらか 1 濃度を 103 週間投与し、その後更に 1 週間観察した。夫々の対照として無処理の雌雄各 50 匹のラット及びマウスを用いた。全生存ラット及びマウスは 104 週時に屠殺した。

二酸化チタンの投与による雌雄ラット及びマウスの平均体重には影響は認められなかった。白色便以外には、二酸化チタン投与に関連したと思われる一般症状は認められなかった。バイオアッセイ終了時の雌雄ラット及び雄マウスの生存率には被験物質の影響は認められなかった；雌マウスの死亡率は投与に関連していた。投与群及び対照群の雌雄のラット及びマウスの多くが、生存後期に発現する腫瘍を発生させるリスクを持っていた。

雌ラットにおいては甲状腺の C-cell 腺腫あるいは悪性腫瘍が投与に関連した(P＝0.013)率で発現した、しかしブンフェローニの分類で求められている P=0.025 のレベルに合うような高い(高用量群と対照群の直接比較で P=0.043)ものではなかった(対照群；1/48、低用量群；0/47、高用量群；6/44)。このため、甲状腺のこれらの腫瘍は被験物質投与に関連したものとは考えられなかった。

雌雄のマウスにおいては、投与群の腫瘍の頻度は夫々に対応する対照群に比較して有意に高いものではなかった。

本バイオアッサイの条件下では、Fisher 344 系ラット及び B6C3F1 系マウスに対して二酸化チタンは経口投与により発がん性はないと結論された。

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BIOASSAY OF TITANIUM DIOXIDE FOR POSSIBLE CARCINOGENICITY

CAS No. 13463-67-7

NCI-CG-TR-97

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

BIOASSAY OF

TITANIUM DIOXIDE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
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Bethesda, Maryland 20014

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FOREWORD: This report presents the results of the bioassay of titanium dioxide 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 greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as 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 that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

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

The NCI project officers who were responsible for selecting the protocols used in this bioassay were Drs. N. P Page[1,2] and C. Cueto[1]. The principal investigators were Drs. M. B. Powers[3] and R. W. Voelker[3]. Ms. K. J. Petrovics[3] was responsible for data management, and Mr. G. Najarian[3] for animal care. Histopathologic examinations were performed by Drs. D. A. Banas[3] and R. H. Habermann[3] and reviewed by Dr. Voelker, and the diagnoses included in this report represent their interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[4]. The statistical analyses were performed by Dr. J. R. Joiner[5] and Ms. P. L. Yong[5], using methods selected for the bioassay program by Dr. J. J. Gart[6]. Chemicals used in this bioassay were analyzed at Midwest Research Institute under the direction of Dr. E. Murrill[7], and feed mixtures containing the test chemical were analyzed at Hazleton Laboratories by Dr. C. L. Guyton[3] and Mr. E. Missaghi[3]. The results of these analyses were reviewed by Dr. S. S. Olin[5].

This report was prepared at Tracor Jitco[5] in collaboration with Hazleton Laboratories and NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Waitz, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

The following other scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Dawn G. Goodman[8], Dr. Richard A. Griesemer, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Robert A. Squire[9], Dr. Sherman Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of titanium dioxide for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats and B6C3F1 mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered titanium dioxide in the diet at one of two doses, either 25,000 or 50,000 ppm, for 103 weeks and then observed for 1 additional week. Matched controls consisted of 50 untreated rats of each sex and 50 untreated mice of each sex. All surviving rats and mice were killed at 104 weeks.

Administration of the titanium dioxide had no appreciable effect on the mean body weights of rats or mice of either sex. With the exception of white feces, there was no other clinical sign that was judged to be related to the administration of titanium dioxide. Survival of the rats and the male mice at the end of the bioassay was not affected by the test chemical; mortality in female mice was dose related. Sufficient numbers of dosed and control rats and mice of each sex were at risk for development of late-appearing tumors.

In the female rats, C-cell adenomas or carcinomas of the thyroid occurred at incidences that were dose related (P = 0.013), but were not high enough (P = 0.043 for direct comparison of the high-dose group with the control group) to meet the level of P = 0.025 required by the Bonferroni criterion (controls 1/48, low-dose 0/47, high-dose 6/44). Thus, these tumors of the thyroid were not considered to be related to the administration of the test chemical.

In the male and female mice, no tumors occurred in dosed groups at incidences that were significantly higher than those for corresponding control groups.

It is concluded that under the conditions of this bioassay, titanium dioxide was not carcinogenic by the oral route for Fischer 344 rats or B6C3F1 mice.

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I. INTRODUCTION

Titanium dioxide (CAS 13463-67-7; NCI C04240) is a white pigment possessing great covering or opacifying power. It exists in three crystalline forms: anatase, brookite, and rutile, but only the anatase variety is used as a food color additive (Noonan, 1975). Titanium dioxide has been in use since 1918, although the market was greatly expanded after 1948 when the need for titanium led to technological advancements in ore processing (Bomberger, 1969). In 1977, the production volume for titanium dioxide in the United States was 800,000 tons. The majority of this was produced for pigmentary applications; 50% for paints and other protective coatings, 20% for paper, and 12% for plastics (Greek, 1977). Titanium dioxide is used as a color additive in foods (anatase) (FDA, 1976a), and in topical and oral drugs (FDA, 1976b). In the cosmetics industry, it is used as a whitener in a wide variety of products including aftershave powders, bath powders, face powders, depilatories, deodorants, fingernail coatings, beauty masks, cleansing creams, eye makeup, foundations, lipsticks, and skin lighteners (Bell, 1972; Saute, 1972; Farber, 1972; Barry, 1972; Doviak, 1972; Fiedler, 1972; Lauffer, 1972; Wetterhahn, 1972; Plechner, 1972; Shevlin, 1972). It has been formulated in sunscreens as a physical light-blocking agent (MacLeod and Frain-Bell, 1975).

Although its refractive index accounts for its most important use as a white pigment, titanium dioxide has important nonpigmentary uses. These include use as a catalyst, a dielectric in capacitors, an anticorrosive in vitreous enamel coatings, a welding rod coating, a source of titanium metal, and a gem (Stanley, 1969).

A titanium coordination complex was shown to be carcinogenic in rats and mice by intramuscular injection (Furst and Haro, 1970). The compound tested was a metallocene, a sandwich arrangement of the metal between two cyclopentadiene molecules. Titanium dioxide was selected for study in the Carcinogenesis Testing Program because this result stimulated an interest in the carcinogenicity of other titanium compounds, such as the dioxide, which was in wide commercial use.

II. MATERIALS AND METHODS

A. Chemical

Three lots of titanium dioxide anatase, designated Unitane® 0-220, were obtained from American Cyanamid Company, Wayne, New Jersey. The manufacturer's specification was 98% minimum TiO_2. The identity and purity of each batch was determined by Midwest Research Institute, Kansas City, Missouri. The moisture content of each batch was < 0.4%.

Atomic absorption analysis for titanium matched the theoretical value in Lot No. 402110C46 (used in the 90-day subchronic toxicity studies), was about 1.6% high in Lot No. 402129A29 (used from weeks 0-51 in the chronic studies), and was 1.5% low in Lot No. 402129B20 (used from weeks 52-103 in the chronic studies). Lot No. 402110C46 also contained 0.15% aluminum by atomic absorption. Other impurities in the 0.1-1.0% range (identified by spark source mass spectrometry) were niobium and chlorine (Lot Nos. 402129A29 and 402129B20), phosphorus (all three lots), silicon (Lot Nos. 402110C46 and 402129B20), calcium (Lot No. 402110C46), and potassium (Lot No. 402129B20). Infrared spectra of all lots were identical to the spectrum given in the literature (Kammori et al., 1967).

B. Dietary Preparation

A quantity of the bulk chemical was sifted to remove any large particles, and the amount required for each dose mixture was weighed out under a hood. This quantity was then incorporated into the basal diet of Wayne® Lab Blox animal meal (Allied Mills, Inc., Chicago, Ill.) by thorough mixing in a Patterson-Kelly twin-shell blender equipped with an intensifier bar. Corn oil (Duke's, C. F. Sauer Co., Richmond, Va.) was added to the dosed diets and to the diets for the matched controls to give a final concentration of 2%. Diets were prepared once per week and stored at room temperature until used.

As a quality control measure, selected samples from freshly prepared mixtures were stored at 4°C and aliquots from these samples, containing approximately 50 micrograms of titanium dioxide were later analyzed for titanium dioxide by the method described by the Association of Official Analytical Chemists (1975). The results of these analyses are summarized in Appendix G. At each dietary concentration, the mean value obtained by the analytical method was within 4% of the theoretical value, although the coefficient of variation was nearly 30%. This variation appears to be due to the difficulty in obtaining a homogeneous mix of a fine powder in feed.

C. Animals

Fischer 344 rats and B6C3F1 mice were obtained from the Frederick Cancer Research Center, Frederick, Maryland, through contracts with the Division of Cancer Treatment, National Cancer Institute. On arrival at the laboratory, the rats were quarantined for 30 days and the mice for 15 days, determined to be free from observable disease or parasites, and assigned to the dosed or control groups based on initial individual body weight, so that the of mean animal body weights per group were approximately equal.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature was generally maintained at 20-24°C and the relative humidity at 45-55%. Incoming air was filtered through 2-inch-thick disposable fiberglass filters at a rate that allowed 12 changes of room air per hour. Lighting was provided on a 12-hour-per-day cycle.

The rats and mice were each housed in polycarbonate cages covered with stainless steel cage lids and non-woven fiber filter bonnets (Filtek, Appleton, Wis.). The rats were initially housed five per cage; however, at week 48, the males were divided into groups of two or three per cage. The mice were housed five per cage throughout the study.

All cages were furnished with heat-treated hardwood chip bedding (Sani-Chips®, Shurfire Products Corporation, Beltsville, Maryland); the bedding was changed twice per week. Diets and well water were made available _ad libitum_. Food hoppers were refilled twice per week.

Cages, water bottles, and sipper tubes were sanitized at 81°C twice per week, feed hoppers once per week, and cage racks once per month. An industrial dish washer was used for the water bottles, and sipper tubes; a cage and rack washer was used for the food hoppers, cages, and racks. Acclaim®, a chlorinated detergent, was used. When racks were washed, clean racks containing cages of animals were randomly repositioned in the rooms.

The rats and mice were housed in separate rooms. Control animals were housed in the same room as the respective dosed animals.

Rats administered diets containing titanium dioxide were maintained in the same room as rats being administered the following chemicals:

Rats

Feed Studies

(CAS 89-78-1) dl-menthol
(CAS 119-53-9) benzoin
(CAS 120-61-6) dimethylterephthalate

Gavage Studies

(CAS 127-69-5) sulfisoxazole
(CAS 7488-56-4) selenium disulfide
(CAS 108-60-1) bischloroisopropyl ether

Drinking Water Studies

(CAS 108-95-2) phenol

At week 48, the rats fed titanium dioxide, together with those fed dl-menthol and those fed benzoin, were moved to a separate room for the remainder of the bioassay.

Mice administered diets containing titanium dioxide were maintained in the same room as mice being administered the following chemicals:

Mice

Feed Studies

(CAS 89-78-1) dl-menthol
(CAS 119-53-9) benzoin
(CAS 120-61-6) dimethylterephthalate

Gavage Studies

(CAS 127-69-5) sulfisoxazole
(CAS 7488-56-4) selenium disulfide
(CAS 108-60-1) bischloroisopropyl ether

Drinking Water Studies

(CAS 108-95-2) phenol

The control groups of rats and mice used for the titanium dioxide studies were used also for the dl-menthol studies. The control groups were maintained in the same rooms with the dosed groups.

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses of titanium dioxide, on the basis of which two concentrations (hereinafter referred to as "low" and "high" doses) were selected for administration in the chronic studies. On the basis of results from a 14-day (repeated dose) oral range-finding study, doses of 6,250, 12,500, 25,000, 50,000, or 100,000 ppm were administered in the diet in the subchronic studies. Ten males and 10 females of each species were administered the test chemical at each dose, and 10 males and 10 females received basal diets. Dosed animals received the test compound for 13 consecutive weeks.

In both the rat studies and the mouse studies, there were no deaths, and dosed animals had mean body weight gains that were comparable to those of the controls. No gross or microscopic pathology was found that could be related to the administration of the test chemical in either the rats or the mice. On the basis of these results, the high dose for both the rats and mice in the chronic studies was set at 50,000 ppm, the maximum amount allowed for use in chronic bioassays in the Carcinogenesis Testing Program, and the low dose was set at 25,000 ppm.

F. Designs of Chronic Studies

The test groups, doses administered, and times on study of the chronic feeding studies are shown in table 1.

G. Clinical and Pathological Examinations

All animals were observed twice daily for signs of toxicity. Clinical signs and the presence of palpable masses were recorded every week. Mean body weights and food consumption were recorded every 2 weeks for the first 12 weeks and every month thereafter.

Animals that were moribund and those that survived to the termination of the study were killed by exsanguination under sodium pentobarbital anesthesia (Diabutal®, Diamond Laboratories, Inc., Des Moines, Iowa). The sodium pentobarbital was injected intraperitoneally at a volume of 0.3 to 0.5 ml for the rats and 0.03 to 0.05 ml for the mice.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions

Table 1. Design of Titanium Dioxide Chronic Feeding Studies in Rats and Mice

Sex and Test Group	Initial No. of Animals[a]	Titanium Dioxide Doses[b] (ppm)	Time on Study: Dosed (weeks)	Time on Study: Observed (weeks)
Male				
Matched-Control	50	0		104
Low-Dose	50	25,000	103	1
High-Dose	50	50,000	103	1
Female				
Matched-Control	50	0		104
Low-Dose	50	25,000	103	1
High-Dose	50	50,000	103	1

[a]Rats were 64 days of age and mice were 36 days of age when placed on study.

[b]The test chemical was administered 7 days per week in a diet containing 2% corn oil. The control groups received only 2% corn oil in the diet. Diets were available *ad libitum*.

from killed animals and from animals found dead. The tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: brain (frontal cortex and basal ganglia, parietal cortex and thalamus, and cerebellum and pons), pituitary, spinal cord (if neurologic signs were present), eyes (if grossly abnormal), esophagus, trachea, salivary glands, mandibular lymph node, thyroid, parathyroid, heart, thymus, lungs and mainstem bronchi, liver, gallbladder (mice), pancreas, spleen, kidney, adrenal, stomach, small intestine, colon, urinary bladder, prostate or uterus, testes or ovaries, sternebrae, femur, or vertebrae including marrow, mammary gland, tissue masses, and any gross lesion.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals may have been missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study 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) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for 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 is 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) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed 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) 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), was also used when appropriate. Under the assumption of a linear trend, this test determines 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 is 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 an animal died naturally or was 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 with 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 dosed 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 dosed 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 dosed 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% of a large number of identical experiments, the true ratio of the risk in a dosed 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 ($P < 0.025$ 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. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Administration of titanium dioxide had no appreciable effect on the mean body weights of either the male or the female rats (figure 1). The clinical signs observed in the dosed groups were generally comparable to those of the control group and included alopecia, sores, and lacrimating, protruding, and/or pale eyes. From weeks 88 through 104, hunched appearance and thinness were noted more frequently in the dosed males and females than in their respective controls. Urine stains were noted on the dosed rats of each sex. Animals in all of the dosed groups had white feces.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered titanium dioxide in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.

In the male rats, 36/50 (72%) of the high-dose group, 37/50 (74%) of the low-dose group, and 31/50 (62%) of the matched controls

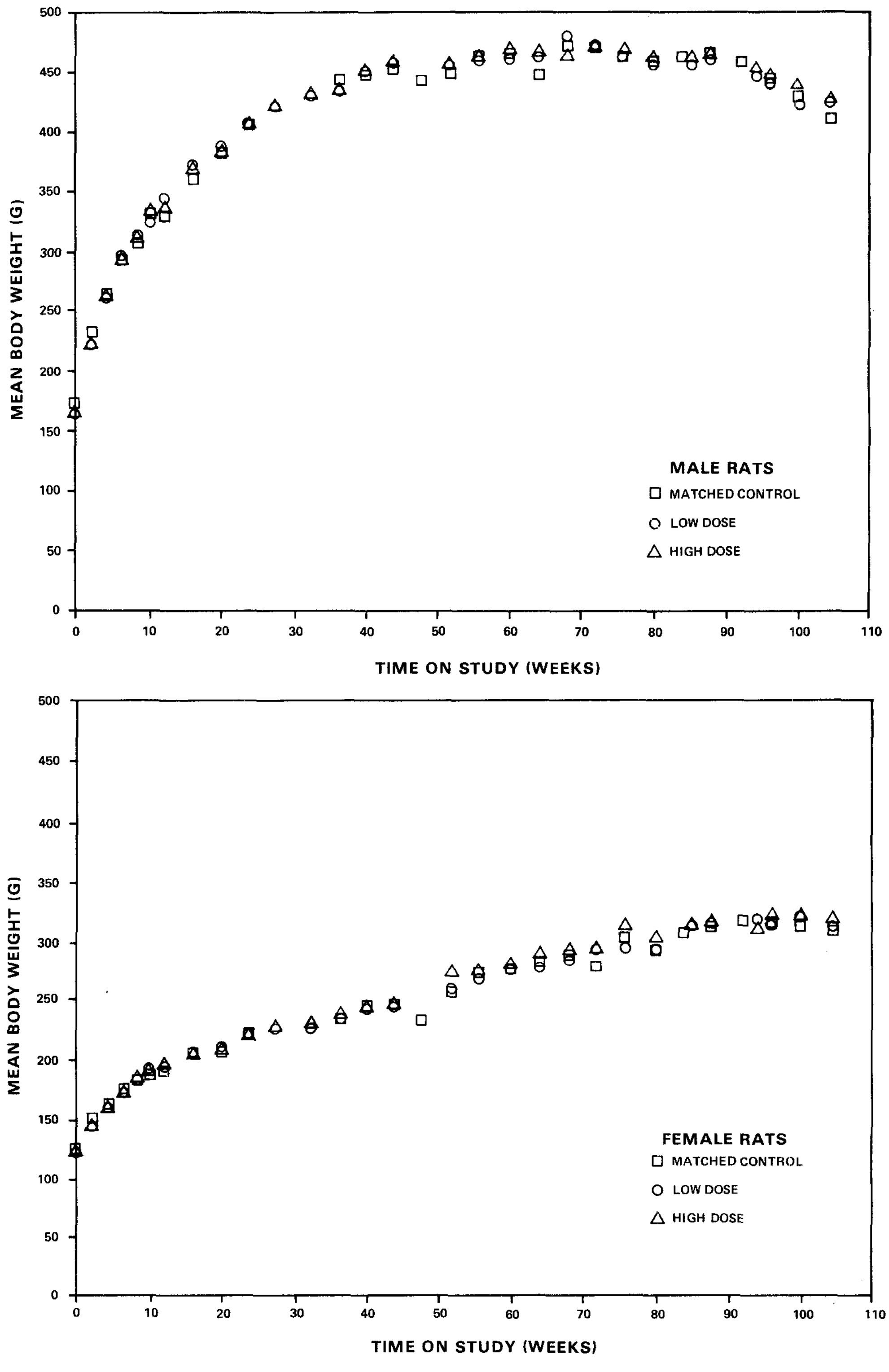


Figure 1. Growth Curves for Rats Administered Titanium Dioxide in the Diet

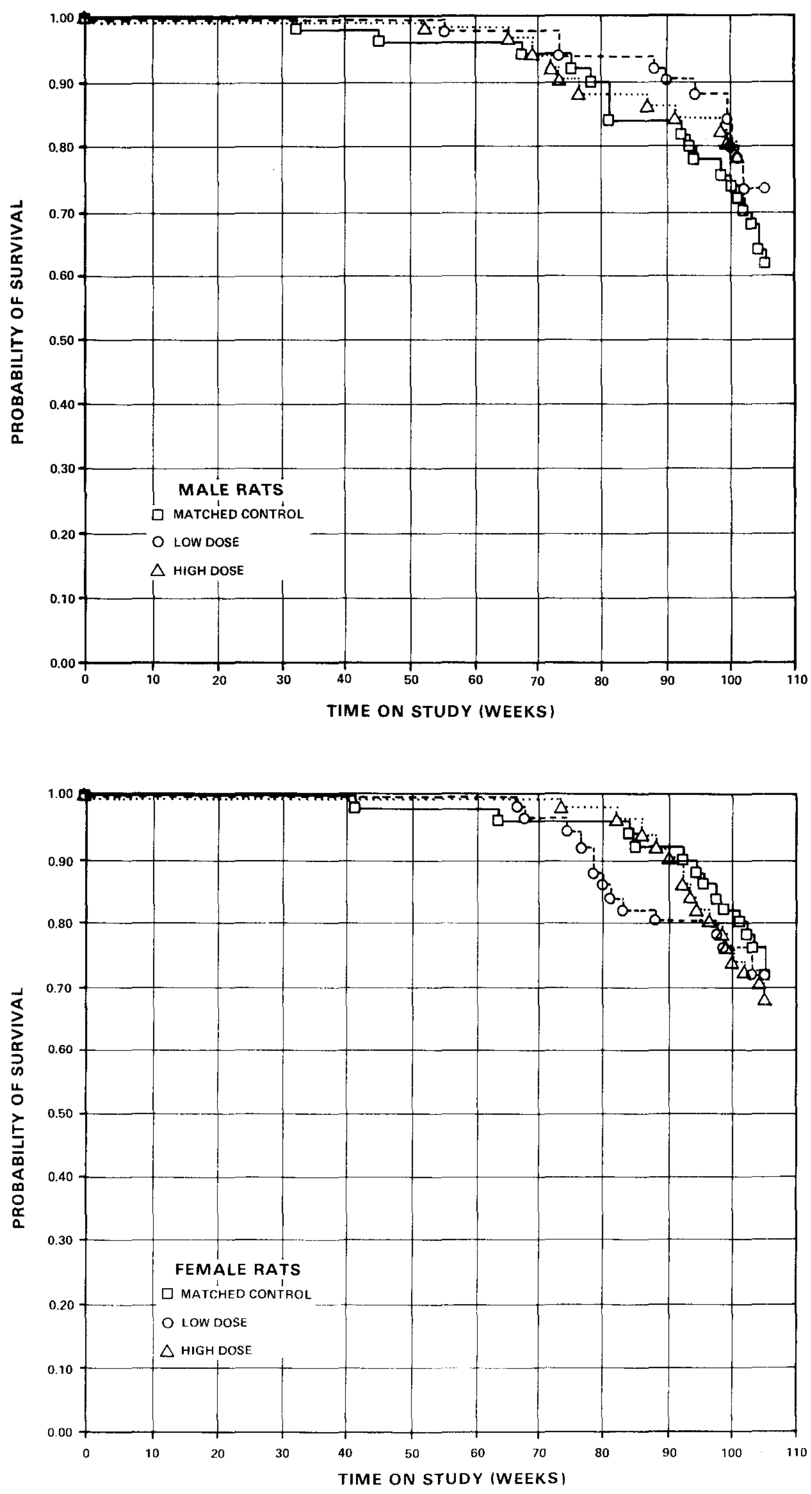


Figure 2. Survival Curves for Rats Administered Titanium Dioxide in the Diet

were alive at week 104. In the females, 34/50 (68%) of the high-dose group, 36/50 (72%) of the low-dose group, and 36/50 (72%) of the matched controls were alive at week 104. Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

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.

Each of the tumor types listed has been encountered previously as a spontaneous lesion, and with only a few exceptions, occurred with no appreciable difference in frequency between control and dosed groups. In the male rats, pheochromocytomas of the adrenal medulla and fibromas of the subcutaneous tissue were observed with slightly greater frequency in dosed groups; however, the number of neoplasms was compatible with incidences of these tumors in historical-control rats of this age and strain. In the female rats, endometrial stromal polyps were observed more frequently in dosed groups than in control groups, but the incidence of lesions is comparable with that in historical controls. Thus, these lesions are not considered to be related to administration of the test chemical.

Inflammatory, degenerative, and hyperplastic lesions that occurred were similar in number and kind to those naturally occurring lesions found in aged Fischer 344 rats.

Based on the histopathologic examination, titanium dioxide was neither toxic nor carcinogenic to Fischer 344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In the male rats, three keratoacanthomas of the skin were observed in the high-dose group, but none in the other two groups studied. Although the result of the Fisher exact test for direct comparison of the incidence in the high-dose group with that in the control group is not significant, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of these tumors is significant ($P = 0.038$).

In the female rats, the result of the Cochran-Armitage test for positive dose-related trend in the combined incidence of C-cell adenomas or carcinomas of the thyroid is significant ($P = 0.013$).

A significant (P = 0.044) departure from linear trend is observed due to the relatively steep increase in this incidence of tumors observed in the high-dose group. The result of the Fisher exact test comparing the incidence in the high-dose group with that in the control group indicates a P value of 0.043, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The results of statistical tests of the incidence of these tumors in the male rats are not significant.

The Fisher exact comparison of the incidence of endometrial stromal polyps of the uterus/endometrium in the low-dose females with that in the corresponding controls indicates a P value of 0.045, which is above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison. The incidence of these tumors in the high-dose group is not significant when compared with that in the control group, and the result of the Cochran-Armitage test for dose-related trend also is not significant.

Significant results in the negative direction are observed in the incidence of leukemia in male rats, in which the incidence in the control group exceeds the incidences in the dosed groups.

In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by titanium dioxide, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Administration of titanium dioxide had no appreciable effect on the mean body weights of either the male or the female mice (figure 3). The clinical signs observed in the dosed groups were comparable with those of the control group and included protrusion of the eyes, bloody crust surrounding the eyes, palpable nodules, tissue masses and/or wart-like lesions, localized sores, irritation and swelling of the testes, hunched appearance, and/or thinness. Alopecia (localized or generalized) was noted in all the control and dosed groups; however, more was observed in the control females than in the dosed females. The areas of alopecia were primarily located around the nose and head and progressed to generalized alopecia in some of the animals. The type of feed-hopper used in this study may have caused the alopecia around the nose. Animals in all of the dosed groups had white feces.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered titanium dioxide in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. In male mice, the result of the Tarone test for dose-related trend in mortality is

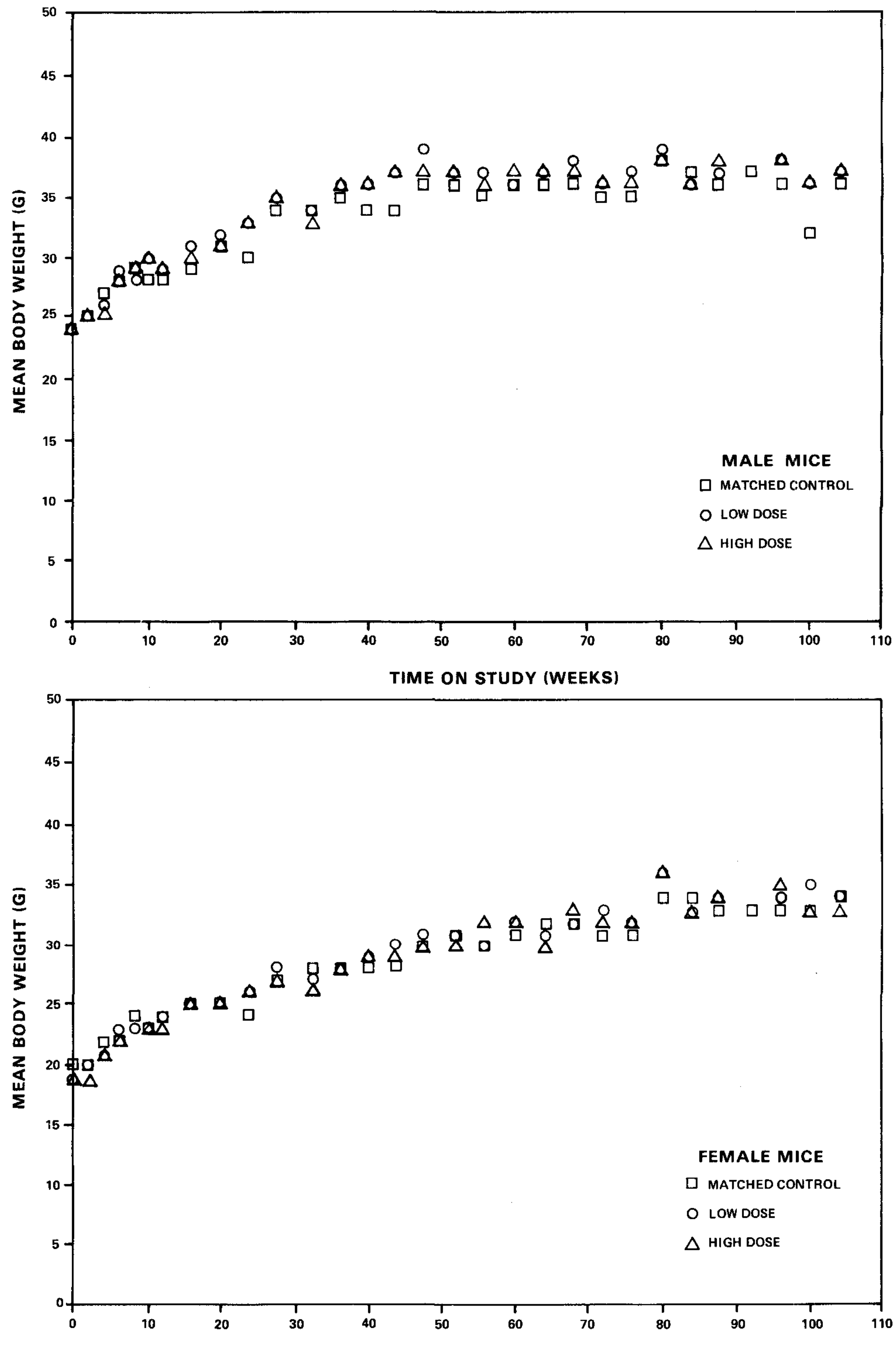
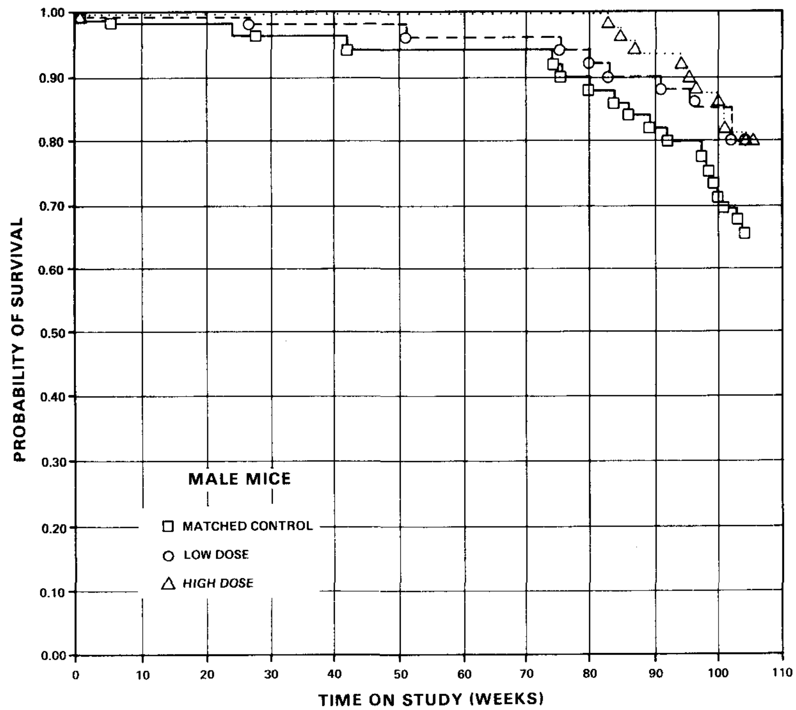


Figure 3. Growth Curves for Mice Administered Titanium Dioxide in the Diet



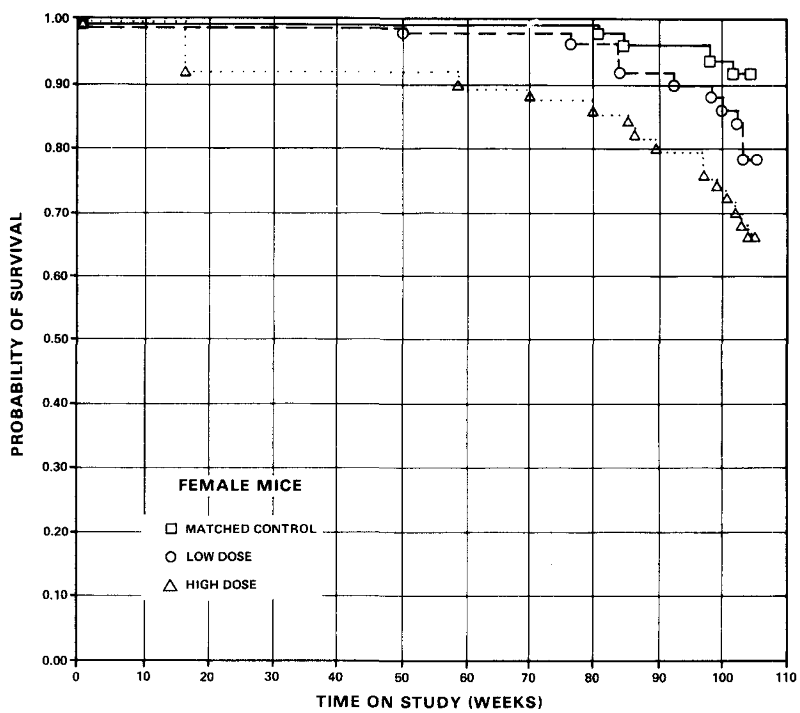


Figure 4. Survival Curves for Mice Administered Titanium Dioxide in the Diet

not significant, but in females, the result of the Tarone test shows a significant (P = 0.001) positive dose-related trend.

Forty out of fifty (80%) of the high-dose males, 40/50 (80%) of the low-dose males, and 32/50 (64%) of the matched-control males were still alive at week 104. In females, 33/50 (66%) of the high-dose group, 39/50 (78%) of the low-dose group, and 45/50 (90%) of the matched controls were alive at week 104. Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

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 neoplasia was observed in both the control mice and dosed mice. These neoplasms were of the usual number and type observed in mice of this age and strain. A slightly increased number of hepatocellular carcinomas was observed in the high-dose males; however, the incidence of tumors was not increased over that observed in historical-control groups of mice of this age and strain.

Degenerative, proliferative, and inflammatory lesions were also of the usual number and kind observed in aged B6C3F1 mice.

Based on the histopathologic examination, titanium dioxide was neither toxic nor carcinogenic to B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The results of the Cochran-Armitage test for positive dose-related trend in incidences of tumors and those of the Fisher exact test for higher incidences of tumors in dosed groups than in control groups are not significant for any type of tumor occurring in either sex. A significant trend ($P = 0.037$) in the negative direction is observed in the incidence of follicular-cell adenomas of the thyroid in female mice, in which the incidence in the control group exceeds the incidences in the dosed groups. The results of the Fisher exact test ($P = 0.035$ in the negative direction) for the comparison of the incidence of combined lymphomas and leukemias in the female low-dose group with that in the corresponding controls are above that of 0.025

required for significance in multiple comparisons. This negative result may be accounted for by the difference in survival, since the dosed animals did not live as long as the control animals.

In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by titanium dioxide, which could not be detected under the conditions of this test.

DISCUSSION

Based on growth rate, mortality, and other clinical signs, there was essentially no evidence of toxicity of titanium dioxide in the dosed rats or dosed mice. Administration of the test chemical had no appreciable effect on the mean body weights of either male or female rats with the exception of white feces, there was no other clinical sign that was judged to be related to the administration of titanium dioxide. Survival of the male and female rats and of the male mice at the end of the bioassay was not affected by the test chemical; survival of the high-dose female mice was shorter than that of the low-dose and control groups. Sufficient numbers of dosed and control rats and mice of each sex were at risk for development of late-appearing tumors. Although little or no effect on weight gain and survival could be attributed to titanium dioxide, except in female mice, the doses were considered to approximate the maximum that could be administered and still not affect the nutritional quality of the diet. This is consistent with the guidelines for carcinogenesis bioassay in the Carcinogenesis Testing Program (Sontag et al., 1976).

In the female rats, C-cell adenomas or carcinomas of the thyroid occurred at incidences that were dose related ($P = 0.013$), but not high enough ($P = 0.043$ for direct comparison of the high-dose group with the control group) to meet the level of P = 0.025 required by the Bonferroni criterion (controls 1/48, low-dose 0/47, high-dose 6/44). Thus, the tumors of the thyroid are not considered to be related to administration of the test chemical. Also in the females, endometrial stromal polyps of the endometrium/uterus occurred at higher incidences in the dosed groups than in the controls, but the incidences were not dose related and were not high enough (P = 0.045 for direct comparison of the low-dose group with the control group) to meet the requirements of the Bonferroni criterion (controls 7/50, low-dose 15/50, high-dose 10/50).

In the male and female mice, no tumors occurred in dosed groups at incidences that were significantly higher than those in corresponding control groups.

In other studies, no adverse pulmonary effects were found when Wistar rats were administered titanium dioxide by inhalation (Christie et al., 1963), and no evidence of carcinogenicity was found when Swiss albino mice were administered potassium titanium oxalate at a concentration of 5 ppm titanium in drinking water for the life span of the mice (Schroeder et al., 1964). When titanium was administered to Fischer 344 rats and to DBA/2, C57BL/6, or Swiss albino mice by intramuscular injection as titanocene, a complex of titanium with cyclopentadiene, a variety of neoplasms developed at the site of injection and in organs some distance away (Furst and Haro, 1969, 1970).

It is concluded that under the conditions of this bioassay, titanium dioxide was not carcinogenic for Fischer 344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED TITANIUM DIOXIDE IN THE DIET

TABLE A1.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		2 (4%)
BASAL-CELL CARCINOMA		1 (2%)	
KERATOACANTHOMA			3 (6%)
*SUBCUT TISSUE	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		
BASAL-CELL CARCINOMA		1 (2%)	
SARCOMA, NOS			1 (2%)
FIBROMA	1 (2%)	5 (10%)	5 (10%)
FIBROSARCOMA	1 (2%)	2 (4%)	
LIPOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
HEMANGIOPERICYTOMA, MALIGNANT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
HEMANGIOPERICYTOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
GRANULOCYTIC LEUKEMIA		2 (4%)	1 (2%)
MONOCYTIC LEUKEMIA	14 (29%)	6 (12%)	5 (10%)
#SPLEEN	(49)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		3 (6%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(48)	(45)	(28)
CARCINOMA,NOS		1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)		
HEPATOCELLULAR CARCINOMA		1 (2%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)
#CECUM	(49)	(46)	(48)
FIBROSARCOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
MIXED TUMOR, BENIGN			1 (2%)
#URINARY BLADDER	(48)	(42)	(45)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(46)
CHROMOPHOBE ADENOMA	5 (10%)	10 (20%)	7 (15%)
#ADRENAL	(49)	(49)	(50)
PHEOCHROMOCYTOMA	7 (14%)	9 (18%)	14 (28%)
#THYROID	(49)	(49)	(50)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	1 (2%)
C-CELL ADENOMA		3 (6%)	
C-CELL CARCINOMA	4 (8%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(49)	(50)	(50)
ISLET-CELL ADENOMA	1 (2%)	2 (4%)	2 (4%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
FIBROADENOMA	1 (2%)	1 (2%)	3 (6%)
*PREPUTIAL GLAND	(49)	(50)	(50)
CARCINOMA,NOS	2 (4%)	5 (10%)	6 (12%)
#TESTIS	(49)	(49)	(50)
INTERSTITIAL-CELL TUMOR	44 (90%)	46 (94%)	41 (82%)
INTERSTITIAL-CELL TUMOR, MALIGNA	1 (2%)		
*EPIDIDYMIS	(49)	(50)	(50)
INTERSTITIAL-CELL TUMOR, INVASIV	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA		2 (4%)	
MUSCULOSKELETAL SYSTEM			
*BONE	(49)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
*SKELETAL MUSCLE	(49)	(50)	(50)
OSTEOSARCOMA, INVASIVE	1 (2%)		
BODY CAVITIES			
*TUNICA VAGINALIS	(49)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
MESOTHELIOMA, NOS	2 (4%)		
MESOTHELIOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	18	11	10
MORIBUND SACRIFICE	1	2	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	31	37	36
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	50	49
TOTAL PRIMARY TUMORS	90	106	100
TOTAL ANIMALS WITH BENIGN TUMORS	46	47	47
TOTAL BENIGN TUMORS	59	80	77
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	23	18
TOTAL MALIGNANT TUMORS	28	26	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	1
TOTAL SECONDARY TUMORS	3	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3		1
TOTAL UNCERTAIN TUMORS	3		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 ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)		3 (6%)
*SUBCUT TISSUE	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	
FIBROMA	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
GRANULOCYTIC LEUKEMIA		1 (2%)	1 (2%)
MONOCYTIC LEUKEMIA	10 (20%)	10 (20%)	11 (22%)
#CERVICAL LYMPH NODE	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
NEOPLASTIC NODULE	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(50)	(50)	(48)
SQUAMOUS CELL PAPILLOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(47)	(47)
CARCINOMA,NOS		3 (6%)	3 (6%)
CHROMOPHOBE ADENOMA	28 (58%)	26 (55%)	31 (66%)
CHROMOPHOBE CARCINOMA			1 (2%)
#ADRENAL	(50)	(49)	(49)
CORTICAL ADENOMA		2 (4%)	
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
#THYROID	(48)	(47)	(44)
FOLLICULAR-CELL ADENOMA	2 (4%)		
C-CELL ADENOMA			2 (5%)
C-CELL CARCINOMA	1 (2%)		4 (9%)
#PANCREATIC ISLETS	(50)	(50)	(49)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS	1 (2%)	2 (4%)	2 (4%)
CYSTADENOMA, NOS	1 (2%)		
FIBROADENOMA	20 (40%)	14 (28%)	19 (39%)
*PREPUTIAL GLAND	(50)	(50)	(49)
CARCINOMA,NOS	2 (4%)	2 (4%)	3 (6%)
ADENOMA, NOS		1 (2%)	
#UTERUS	(50)	(50)	(49)
CARCINOMA,NOS			1 (2%)
FIBROMA		1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL POLYP	6 (12%)	15 (30%)	10 (20%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
SARCOMA, NOS	1 (2%)		
ENDOMETRIAL STROMAL POLYP	1 (2%)		
#OVARY	(49)	(49)	(49)
FIBROMA	1 (2%)		
SEMINOMA/DYSGERMINOMA	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(48)	(48)	(49)
CARCINOMA, NOS, METASTATIC		2 (4%)	2 (4%)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
CHROMOPHOBE CARCINOMA, METASTATI			1 (2%)
GLIOMA, NOS	1 (2%)		
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
*EAR CANAL	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(49)
SARCOMA, NOS			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	11	12	14
MORIBUND SACRIFICE	3	2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	36	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	41	43	46
TOTAL PRIMARY TUMORS	83	86	96
TOTAL ANIMALS WITH BENIGN TUMORS	38	37	41
TOTAL BENIGN TUMORS	62	63	66
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	20	24
TOTAL MALIGNANT TUMORS	20	23	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3	5
TOTAL SECONDARY TUMORS	1	3	6
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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

TABLE B1.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	47	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(47)	(49)	(49)
FIBROMA		1 (2%)	
*SUBCUT TISSUE	(47)	(49)	(49)
SEBACEOUS ADENOMA			1 (2%)
FIBROMA	4 (9%)	3 (6%)	1 (2%)
FIBROSARCOMA	8 (17%)	8 (16%)	4 (8%)
HEMANGIOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(46)	(49)	(49)
HEPATOCELLULAR CARCINOMA, METAST		2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (11%)	2 (4%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(47)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (9%)	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	3 (6%)	5 (10%)
GRANULOCYTIC LEUKEMIA		2 (4%)	
#MESENTERIC L. NODE	(47)	(48)	(48)
HEMANGIOMA		2 (4%)	
HEMANGIOSARCOMA		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(46)	(49)	(49)
HEMANGIOSARCOMA	1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*INTESTINAL TRACT	(47)	(49)	(49)
CARCINOMA, NOS			1 (2%)
#LIVER	(47)	(47)	(49)
HEPATOCELLULAR CARCINOMA	8 (17%)	9 (19%)	14 (29%)
HEMANGIOSARCOMA			1 (2%)
#SMALL INTESTINE	(47)	(49)	(49)
CARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
*URETHRA	(47)	(49)	(49)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(46)	(49)	(48)
PHEOCHROMOCYTOMA		1 (2%)	2 (4%)
#THYROID	(43)	(45)	(45)
FOLLICULAR-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*TESTIS	(47)	(49)	(48)
HEMANGIOMA			2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(47)	(49)	(49)
ADENOMA, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(47)	(49)	(49)
MESOTHELIOMA, NOS	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	17	10	10
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED	1		
TERMINAL SACRIFICE	32	40	40
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	29	25	28
TOTAL PRIMARY TUMORS	36	37	38
TOTAL ANIMALS WITH BENIGN TUMORS	10	8	11
TOTAL BENIGN TUMORS	10	10	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	22	23
TOTAL MALIGNANT TUMORS	25	27	26
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1
TOTAL SECONDARY TUMORS		2	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 B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(49)	(50)	(50)
TRICHOEPITHELIOMA			1 (2%)
FIBROSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)
FIBROSARCOMA, METASTATIC		1 (2%)	
LEIOMYOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	6 (12%)	4 (8%)	7 (14%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	12 (24%)	7 (14%)	4 (8%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)		
GRANULOCYTIC LEUKEMIA			2 (4%)
#SPLEEN	(49)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#CERVICAL LYMPH NODE	(48)	(47)	(47)
HEMANGIOSARCOMA	1 (2%)		
#THYMUS	(23)	(27)	(34)
FIBROSARCOMA, METASTATIC		1 (4%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
HEPATOCELLULAR CARCINOMA	1 (2%)	3 (6%)	3 (6%)
*PANCREAS	(49)	(50)	(50)
FIBROSARCOMA, METASTATIC		1 (2%)	
*STOMACH	(48)	(50)	(49)
LEIOMYOSARCOMA	1 (2%)		
#LARGE INTESTINE	(48)	(50)	(49)
LEIOMYOSARCOMA, METASTATIC	1 (2%)		
URINARY SYSTEM			
*KIDNEY	(49)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
LEIOMYOSARCOMA, METASTATIC	1 (2%)		
#URINARY BLADDER	(47)	(45)	(45)
LEIOMYOSARCOMA, METASTATIC	1 (2%)		
ENDOCRINE SYSTEM			
*PITUITARY	(33)	(40)	(33)
CHROMOPHOBE ADENOMA	3 (9%)	4 (10%)	2 (6%)
#THYROID	(43)	(41)	(44)
FOLLICULAR-CELL ADENOMA	3 (7%)		
C-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	3 (6%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(48)	(49)	(49)
LEIOMYOSARCOMA, METASTATIC	1 (2%)		
ENDOMETRIAL STROMAL POLYP		1 (2%)	
HEMANGIOSARCOMA	1 (2%)		
#OVARY	(47)	(47)	(47)
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
TERATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(49)	(50)	(50)
CARCINOMA,NOS			1 (2%)
ADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
*MESENTERY	(49)	(50)	(50)
LEIOMYOSARCOMA, METASTATIC	1 (2%)		
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	11	16
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	45	39	33
ANIMAL MISSING	1		

@ INCLUDES AUTOLYZED ANIMALS

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	24	26
TOTAL PRIMARY TUMORS	34	26	32
TOTAL ANIMALS WITH BENIGN TUMORS	6	6	9
TOTAL BENIGN TUMORS	7	6	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	26	19	18
TOTAL MALIGNANT TUMORS	27	20	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	1
TOTAL SECONDARY TUMORS	6	3	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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED TITANIUM DIOXIDE IN THE DIET

TABLE C1.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
METAPLASIA, SQUAMOUS	1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, DIFFUSE		1 (2%)	
GRANULOMA, FOREIGN BODY			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(49)
CONGESTION, NOS		6 (12%)	13 (27%)
HEMORRHAGE		5 (10%)	6 (12%)
INFLAMMATION, SUPPURATIVE			1 (2%)
PNEUMONIA, CHRONIC MURINE	5 (10%)	7 (14%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(50)	(50)
HYPOPLASIA, HEMATOPOIETIC		2 (4%)	
#SPLEEN	(49)	(50)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
FIBROSIS		1 (2%)	2 (4%)
INFARCT, NOS		1 (2%)	1 (2%)
PIGMENTATION, NOS		1 (2%)	1 (2%)
HYPERPLASIA, STROMAL			1 (2%)
HEMATOPOIESIS		1 (2%)	4 (8%)
#LYMPH NODE	(49)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#CERVICAL LYMPH NODE	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#BRONCHIAL LYMPH NODE	(49)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#MESENTERIC L. NODE	(49)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)
THROMBOSIS, NOS			1 (2%)
#THYMUS	(48)	(45)	(28)
EMBRYONAL REST		1 (2%)	
THROMBOSIS, NOS			1 (4%)
HYPERPLASIA, NOS			1 (4%)
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(49)
THROMBOSIS, NOS	1 (2%)		
THROMBUS, ORGANIZED		1 (2%)	
INFLAMMATION, CHRONIC		11 (22%)	1 (2%)
FIBROSIS	1 (2%)	8 (16%)	12 (24%)
DEGENERATION, NOS	1 (2%)		
#MYOCARDIUM	(49)	(50)	(49)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
DEGENERATION, NOS	1 (2%)		
*AORTA	(49)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#LIVER	(49)	(50)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
PELIOSIS HEPATIS	1 (2%)		
DEGENERATION, LIPOID			1 (2%)
NECROSIS, NOS			2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL			1 (2%)
INFARCT, NOS		1 (2%)	3 (6%)
METAMORPHOSIS FATTY	1 (2%)		
FOCAL CELLULAR CHANGE		3 (6%)	1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(50)
NECROSIS, NOS	1 (2%)	1 (2%)	
*BILE DUCT	(49)	(50)	(50)
FIBROSIS		1 (2%)	
HYPERPLASIA, NOS		21 (42%)	27 (54%)
#PANCREAS	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
PERIARTERITIS	2 (4%)	5 (10%)	3 (6%)
PIGMENTATION, NOS		1 (2%)	
ATROPHY, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREATIC DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
#PANCREATIC ACINUS	(49)	(50)	(50)
ATROPHY, NOS			2 (4%)
#STOMACH	(49)	(50)	(50)
ULCER, FOCAL		5 (10%)	4 (8%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERKERATOSIS		2 (4%)	
ACANTHOSIS		2 (4%)	
#SMALL INTESTINE	(49)	(50)	(47)
ULCER, FOCAL		1 (2%)	
#ILEUM	(49)	(50)	(47)
MECKELS DIVERTICULUM			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
#COLON	(49)	(46)	(48)
PARASITISM	3 (6%)	13 (28%)	6 (13%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
HYDRONEPHROSIS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS			2 (4%)
CONGESTION, NOS			1 (2%)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	29 (59%)	45 (90%)	43 (86%)
PERIARTERITIS			1 (2%)
AMYLOIDOSIS	1 (2%)		
PIGMENTATION, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(46)
CYST, NOS			1 (2%)
HEMORRHAGE			1 (2%)
ANGIECTASIS			1 (2%)
#ADRENAL	(49)	(49)	(50)
ANGIECTASIS			1 (2%)
#ADRENAL CORTEX	(49)	(49)	(50)
DEGENERATION, NOS	1 (2%)		
#ADRENAL MEDULLA	(49)	(49)	(50)
HYPERPLASIA, NOS			1 (2%)
#THYROID	(49)	(49)	(50)
CYSTIC FOLLICLES			1 (2%)
HYPERPLASIA, C-CELL		1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#PANCREATIC ISLETS	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
GALACTOCELE		2 (4%)	1 (2%)
*PREPUTIAL GLAND	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST		2 (4%)	
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#PROSTATE	(47)	(43)	(45)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, SUPPURATIVE	1 (2%)	2 (5%)	8 (18%)
INFLAMMATION, CHRONIC			1 (2%)
*SEMINAL VESICLE	(49)	(50)	(50)
ATROPHY, NOS		6 (12%)	10 (20%)
#TESTIS	(49)	(49)	(50)
ATROPHY, NOS	3 (6%)	5 (10%)	7 (14%)
HYPERPLASIA, INTERSTITIAL CELL		3 (6%)	4 (8%)
*EPIDIDYMIS	(49)	(50)	(50)
NECROSIS, FAT		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
HYDROCEPHALUS, NOS			1 (2%)
ABSCESS, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(49)	(50)	(50)
NECROSIS, FAT		4 (8%)	2 (4%)
*PERITONEAL CAVITY	(49)	(50)	(50)
NECROSIS, FAT			3 (6%)
*PERICARDIUM	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
*MESENTERY	(49)	(50)	(50)
PERIARTERITIS	1 (2%)	1 (2%)	
NECROSIS, FAT	2 (4%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
DIAPHRAGM			
HERNIA, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF	1		
AUTOLYSIS/NO NECROPSY	1		

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

TABLE C2.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
ABSCESS, NOS			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(49)
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
CONGESTION, NOS		12 (24%)	10 (20%)
HEMORRHAGE	1 (2%)	8 (16%)	9 (18%)
PNEUMONIA, CHRONIC MURINE	3 (6%)	3 (6%)	1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
EPITHELIALIZATION		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(48)
FIBROSIS		1 (2%)	1 (2%)
PIGMENTATION, NOS			2 (4%)
ATROPHY, NOS		4 (8%)	1 (2%)
HEMATOPOIESIS		2 (4%)	1 (2%)
#CERVICAL LYMPH NODE	(50)	(50)	(49)
INFLAMMATION, NOS	3 (6%)		1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(50)	(50)	(49)
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS		1 (2%)	
#THYMUS	(48)	(35)	(24)
CYST, NOS		1 (3%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CONGESTION, NOS		2 (6%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(49)
FIBROSIS		10 (20%)	5 (10%)
CALCIFICATION, NOS		1 (2%)	1 (2%)
#MYOCARDIUM	(50)	(50)	(49)
FIBROSIS	1 (2%)		
DEGENERATION, NOS	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
CONGESTION, NOS		5 (10%)	2 (4%)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
DEGENERATION, LIPOID		3 (6%)	3 (6%)
METAMORPHOSIS FATTY	2 (4%)		1 (2%)
FOCAL CELLULAR CHANGE	3 (6%)	5 (10%)	3 (6%)
ANGIECTASIS	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(49)	(49)
NECROSIS, NOS			1 (2%)
*BILE DUCT	(50)	(50)	(49)
FIBROSIS			1 (2%)
HYPERPLASIA, NOS		14 (28%)	14 (29%)
#PANCREATIC ACINUS	(50)	(50)	(49)
ATROPHY, NOS		2 (4%)	1 (2%)
ATROPHY, FOCAL			3 (6%)
#STOMACH	(50)	(50)	(48)
INFLAMMATION, NOS		1 (2%)	1 (2%)
ULCER, NOS	1 (2%)		
ULCER, FOCAL	1 (2%)	4 (8%)	3 (6%)
CALCIFICATION, NOS		1 (2%)	2 (4%)
HYPERPLASIA, BASAL CELL		1 (2%)	
HYPERKERATOSIS			2 (4%)
ACANTHOSIS			2 (4%)
#GASTRIC SUBMUCOSA	(50)	(50)	(48)
EDEMA, NOS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#COLON	(50)	(50)	(49)
ADHESION, NOS			1 (2%)
PARASITISM		5 (10%)	2 (4%)
#COLONIC SUBMUCOSA	(50)	(50)	(49)
EDEMA, NOS			1 (2%)
#CECUM	(50)	(50)	(49)
HEMORRHAGE		1 (2%)	
*RECTUM	(50)	(50)	(49)
ADHESION, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
MINERALIZATION			1 (2%)
CONGESTION, NOS		2 (4%)	1 (2%)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	19 (38%)	24 (48%)	26 (53%)
CALCIFICATION, NOS		1 (2%)	2 (4%)
PIGMENTATION, NOS		1 (2%)	16 (33%)
#KIDNEY/PELVIS	(50)	(50)	(49)
INFLAMMATION, NOS	1 (2%)		
#URINARY BLADDER	(47)	(48)	(46)
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(47)	(47)
CYST, NOS	2 (4%)	2 (4%)	4 (9%)
HYPERPLASIA, CHROMOPHOBE-CELL			1 (2%)
#ADRENAL	(50)	(49)	(49)
ANGIECTASIS	1 (2%)	2 (4%)	
#THYROID	(48)	(47)	(44)
HYPERPLASIA, C-CELL		5 (11%)	2 (5%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#PARATHYROID	(31)	(34)	(30)
HYPERPLASIA, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
GALACTOCELE	2 (4%)	14 (28%)	14 (29%)
LACTATION	1 (2%)	6 (12%)	9 (18%)
*VAGINA	(50)	(50)	(49)
INFLAMMATION, NOS	1 (2%)		
#UTERUS	(50)	(50)	(49)
HYDROMETRA	7 (14%)		1 (2%)
CYST, NOS	2 (4%)		
THROMBUS, ORGANIZED	1 (2%)		
HEMORRHAGIC CYST			1 (2%)
PYOMETRA		1 (2%)	1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
HYPERPLASIA, CYSTIC		3 (6%)	1 (2%)
#OVARY/PAROVARIAN	(50)	(50)	(49)
NECROSIS, FAT		1 (2%)	
#OVARY	(49)	(49)	(49)
CYST, NOS	1 (2%)	1 (2%)	
FOLLICULAR CYST, NOS			2 (4%)
PAROVARIAN CYST		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(48)	(48)	(49)
COMPRESSION		3 (6%)	5 (10%)
HYDROCEPHALUS, NOS		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
CATARACT	1 (2%)	1 (2%)	2 (4%)
*EYE/RETINA	(50)	(50)	(49)
ATROPHY, NOS		1 (2%)	3 (6%)
*HARDERIAN GLAND	(50)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(49)
NECROSIS, FAT	3 (6%)	2 (4%)	4 (8%)
*PERITONEAL CAVITY	(50)	(50)	(49)
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
LEUKOCYTOSIS, NOS		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2		
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

TABLE D1.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	47	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	47	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(47)	(49)	(49)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, NOS	3 (6%)		
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HYPERKERATOSIS	2 (4%)		
ACANTHOSIS	2 (4%)		
*SUBCUT TISSUE	(47)	(49)	(49)
EDEMA, NOS			1 (2%)
GRANULOMA, NOS	1 (2%)		
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(46)	(49)	(49)
CONGESTION, NOS			2 (4%)
HEMORRHAGE		1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
PNEUMONIA, CHRONIC MURINE	1 (2%)	5 (10%)	2 (4%)
#LUNG/ALVEOLI	(46)	(49)	(49)
EPITHELIALIZATION		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(47)	(49)	(49)
CONGESTION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		6 (12%)	
HEMATOPOIESIS	3 (6%)	2 (4%)	5 (10%)
#LYMPH NODE	(47)	(48)	(48)
LYMPHANGIECTASIS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(47)	(48)	(48)
LYMPHANGIECTASIS	1 (2%)	12 (25%)	15 (31%)
HEMORRHAGE	1 (2%)		
PERIARTERITIS			1 (2%)
HYPERPLASIA, RETICULUM CELL			4 (8%)
HEMATOPOIESIS		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(46)	(49)	(49)
PERIARTERITIS			1 (2%)
#AURICULAR APPENDAGE	(46)	(49)	(49)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(48)	(47)
INFLAMMATION, NOS		1 (2%)	
#LIVER	(47)	(47)	(49)
CYST, NOS		2 (4%)	1 (2%)
THROMBUS, ORGANIZED			1 (2%)
INFLAMMATION, CHRONIC			2 (4%)
NECROSIS, NOS			8 (16%)
NECROSIS, FOCAL			1 (2%)
ANGIECTASIS			2 (4%)
#LIVER/CENTRILOBULAR	(47)	(47)	(49)
NECROSIS, NOS		1 (2%)	
*BILE DUCT	(47)	(49)	(49)
DILATATION, NOS		2 (4%)	
#PANCREAS	(47)	(49)	(48)
CYST, NOS	1 (2%)		
CYSTIC DUCTS		1 (2%)	
PERIARTERITIS			1 (2%)
#STOMACH	(47)	(49)	(49)
HYPERKERATOSIS	2 (4%)		
ACANTHOSIS	2 (4%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#LARGE INTESTINE	(45)	(49)	(49)
NEMATODIASIS	1 (2%)		3 (6%)
URINARY SYSTEM			
#KIDNEY	(47)	(49)	(49)
INFLAMMATION, CHRONIC		4 (8%)	5 (10%)
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#URINARY BLADDER	(46)	(49)	(49)
POLYP		1 (2%)	
#U.BLADDER/SUBMUCOSA	(46)	(49)	(49)
EDEMA, NOS			1 (2%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(47)	(49)	(49)
HYPERPLASIA, NOS	1 (2%)		
#TESTIS	(47)	(49)	(48)
GRANULOMA, SPERMATIC		1 (2%)	
ATROPHY, NOS		1 (2%)	1 (2%)
*EPIDIDYMIS	(47)	(49)	(49)
NECROSIS, FAT	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(47)	(49)	(49)
INFLAMMATION, NOS	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
VASCULARIZATION	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(47)	(49)	(49)
NECROSIS, FAT	1 (2%)	2 (4%)	
*MESENTERY	(47)	(49)	(49)
PERIARTERITIS			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	8	8	10
AUTO/NECROPSY/HISTO PERF	1	1	
AUTOLYSIS/NO NECROPSY	3	1	1

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

TABLE D2.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
CONGESTION, NOS		4 (8%)	4 (8%)
HEMORRHAGE		1 (2%)	
PNEUMONIA, CHRONIC MURINE	3 (6%)	5 (10%)	5 (10%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(50)	(50)
HEMORRHAGIC CYST		1 (2%)	
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		7 (14%)	
HEMATOPOIESIS		4 (8%)	2 (4%)
#MESENTERIC L. NODE	(48)	(47)	(47)
LYMPHANGIECTASIS		5 (11%)	
HYPERPLASIA, LYMPHOID		5 (11%)	
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
#MYOCARDIUM	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
DEGENERATION, LIPOID		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
INFARCT, NOS			1 (2%)
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
*BILE DUCT	(49)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#PANCREAS	(49)	(50)	(50)
CYST, NOS		1 (2%)	
CYSTIC DUCTS	2 (4%)		1 (2%)
ATROPHY, NOS	1 (2%)		
#PANCREATIC DUCT	(49)	(50)	(50)
CONGENITAL MALFORMATION, NOS		1 (2%)	
#PANCREATIC ACINUS	(49)	(50)	(50)
ATROPHY, NOS			1 (2%)
#STOMACH	(48)	(50)	(49)
ULCER, FOCAL		1 (2%)	2 (4%)
HYPERKERATOSIS	1 (2%)	1 (2%)	1 (2%)
ACANTHOSIS	1 (2%)	1 (2%)	
#SMALL INTESTINE	(49)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LARGE INTESTINE	(48)	(50)	(49)
NEMATODIASIS		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL		3 (6%)	
INFARCT, NOS			2 (4%)
CALCIFICATION, NOS		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(33)	(40)	(33)
CYST, NOS		1 (3%)	
#THYROID	(43)	(41)	(44)
HYPERPLASIA, FOLLICULAR-CELL		2 (5%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
METAPLASIA, SQUAMOUS			1 (2%)
LACTATION			1 (2%)
#UTERUS	(48)	(49)	(49)
HYDROMETRA	6 (13%)	3 (6%)	
THROMBOSIS, NOS		2 (4%)	
PYOMETRA			1 (2%)
ANGIECTASIS		3 (6%)	
#UTERUS/ENDOMETRIUM	(48)	(49)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC	17 (35%)	42 (86%)	38 (78%)
#OVARY	(47)	(47)	(47)
CYST, NOS	10 (21%)		
FOLLICULAR CYST, NOS	1 (2%)	11 (23%)	8 (17%)
PAROVARIAN CYST	1 (2%)	1 (2%)	4 (9%)
HEMORRHAGIC CYST			2 (4%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
MALACIA		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(49)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*HARDERIAN GLAND	(49)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	1	2
ANIMAL MISSING/NO NECROPSY	1		

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED TITANIUM DIOXIDE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Keratoacanthoma of the Skin[b]	0/49 (0)	0/50 (0)	3/50 (6)
P Values[c,d]	P = 0.038	N.S.	N.S.
Relative Risk[f]		--	Infinite
Lower Limit		--	0.590
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	98
Integumentary System: Fibroma of the Skin[b]	1/49 (2)	5/50 (10)	5/50 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		4.900	4.900
Lower Limit		0.577	0.577
Upper Limit		226.749	226.749
Weeks to First Observed Tumor	100	99	69

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Leukemia[b]	14/49 (29)	8/50 (16)	6/50 (12)
P Values[c,d]	P = 0.024(N)	N.S.	P = 0.035(N)
Relative Risk[f]		0.560	0.420
Lower Limit		0.224	0.144
Upper Limit		1.295	1.060
Weeks to First Observed Tumor	81	90	91
All Sites: Hemangiosarcoma[b]	1/49 (2)	1/50 (2)	3/50 (6)
P Vales[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.980	2.940
Lower Limit		0.013	0.246
Upper Limit		75.404	151.180
Weeks to First Observed Tumor	105	73	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	5/48 (10)	10/50 (20)	7/46 (15)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.920	1.461
Lower Limit		0.649	0.430
Upper Limit		6.661	5.433
Weeks to First Observed Tumor	103	88	73
Adrenal: Pheochromocytoma[b]	7/49 (14)	9/49 (18)	14/50 (28)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.286	1.960
Lower Limit		0.464	0.816
Upper Limit		3.742	5.238
Weeks to First Observed Tumor	67	99	101

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma[b]	4/49 (8)	1/49 (2)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.250	0.245
Lower Limit		0.005	0.005
Upper Limit		2.409	2.362
Weeks to First Observed Tumor	81	104	105
Thyroid: C-cell Adenoma or Carcinoma[b]	4/49 (8)	4/49 (8)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.000	0.245
Lower Limit		0.197	0.005
Upper Limit		5.077	2.362
Weeks to First Observed Tumor	81	104	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma or Carcinoma[b]	1/49 (2)	2/50 (4)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.960	2.940
Lower Limit		0.106	0.246
Upper Limit		113.312	151.180
Weeks to First Observed Tumor	105	104	72
Mammary Gland: Fibroadenoma[b]	1/49 (2)	1/50 (2)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.980	2.940
Lower Limit		0.013	0.246
Upper Limit		75.404	151.180
Weeks to First Observed Tumor	105	101	99

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Preputial Gland: Carcinoma, NOS[b]	2/49 (4)	5/50 (10)	6/50 (12)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		2.450	2.940
Lower Limit		0.424	0.558
Upper Limit		24.778	28.662
Weeks to First Observed Tumor	105	73	69
Testis: Interstitial-cell Tumor or Interstitial-cell Tumor, Malignant[b]	45/49 (92)	46/49 (94)	41/50 (82)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.022	0.893
Lower Limit		0.910	0.785
Upper Limit		1.130	1.063
Weeks to First Observed Tumor	78	90	76

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Titanium Dioxide in the Diet[a]

(continued)

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[a]Dosed groups received 25,000 or 50,000 ppm.

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

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative, (N), indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Titanium Dioxide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Squamous-cell Carcinoma[b]	2/50 (4)	1/50 (2)	3/49 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.500	1.531
Lower Limit		0.009	0.183
Upper Limit		9.290	17.671
Weeks to First Observed Tumor	85	80	90
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	3/50 (6)	1/50 (2)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.333	0.340
Lower Limit		0.006	0.007
Upper Limit		3.983	4.062
Weeks to First Observed Tumor	105	105	90

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia[b]	10/50 (20)	13/50 (26)	12/49 (24)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.300	1.224
Lower Limit		0.583	0.536
Upper Limit		2.994	2.863
Weeks to First Observed Tumor	94	66	90
Pituitary: Carcinoma, NOS[b]	0/48 (0)	3/47 (6)	3/47 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		Infinite	Infinite
Lower Limit		0.615	0.615
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	98

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	28/48 (58)	26/47 (55)	31/47 (66)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.948	1.131
Lower Limit		0.647	0.801
Upper Limit		1.390	1.584
Weeks to First Observed Tumor	85	78	73
Thyroid: C-cell Carcinoma[b]	1/48 (2)	0/47 (0)	4/44 (9)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.000	4.364
Lower Limit		0.000	0.454
Upper Limit		19.033	209.675
Weeks to First Observed Tumor	105	--	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma or Carcinoma[b]	1/48 (2)	0/47 (0)	6/44 (14)
P Values[c,d]	P = 0.013	N.S.	P = 0.043
Departure from Linear Trend[e]	P = 0.044		
Relative Risk[f]		0.000	6.545
Lower Limit		0.000	0.841
Upper Limit		19.033	293.404
Weeks to First Observed Tumor	105	--	105
Mammary Gland: Fibroadenoma[b]	20/50 (40)	14/50 (28)	19/49 (39)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.700	0.969
Lower Limit		0.373	0.565
Upper Limit		1.283	1.658
Weeks to First Observed Tumor	98	78	86

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Adenoma or Adenocarcinoma, NOS[b]	1/50 (2)	2/50 (4)	3/49 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		2.000	3.061
Lower Limit		0.108	0.256
Upper Limit		115.621	157.341
Weeks to First Observed Tumor	94	103	88
Preputial Gland: Carcinoma, NOS[b]	2/50 (4)	2/50 (4)	3/49 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.000	1.531
Lower Limit		0.075	0.183
Upper Limit		13.326	17.671
Weeks to First Observed Tumor	105	105	105

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus/Endometrium:			
Endometrial Stromal Polyp[b]	7/50 (14)	15/50 (30)	10/49 (20)
P Values[c,d]	N.S.	P = 0.045	N.S.
Relative Risk[f]		2.143	1.458
Lower Limit		0.907	0.546
Upper Limit		5.663	4.149
Weeks to First Observed Tumor	92	83	90

[a]Dosed groups received 25,000 or 50,000 ppm.

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

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P < 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P < 0.05; otherwise, not significant (N.S.) is indicated.

[d]A negative, (N), indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when P < 0.05 for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED TITANIUM DIOXIDE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Titanium Dioxide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibroma[b]	4/47 (9)	4/49 (8)	1/49 (2)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.959	0.240
Lower Limit		0.189	0.005
Upper Limit		4.867	2.309
Weeks to First Observed Tumor	98	104	104
Integumentary System: Fibrosarcoma of the Subcutaneous Tissue[b]	8/47 (17)	8/49 (16)	4/49 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.959	0.480
Lower Limit		0.342	0.113
Upper Limit		2.692	1.662
Weeks to First Observed Tumor	89	75	95

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	6/46 (13)	3/49 (6)	5/49 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.469	0.782
Lower Limit		0.080	0.202
Upper Limit		2.060	2.868
Weeks to First Observed Tumor	104	102	104
Hematopoietic System: Lymphoma or Leukemia[b]	6/47 (13)	7/49 (14)	5/49 (10)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.119	0.799
Lower Limit		0.348	0.207
Upper Limit		3.742	2.932
Weeks to First Observed Tumor	74	75	101

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	8/47 (17)	9/47 (19)	14/49 (29)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.125	1.679
Lower Limit		0.422	0.729
Upper Limit		3.061	4.183
Weeks to First Observed Tumor	89	102	94

[a]Dosed groups received 25,000 or 50,000 ppm.

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

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P < 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P < 0.05; otherwise, not significant (N.S.) is indicated.

[d]A negative, (N), indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when P < 0.05 for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Titanium Dioxide in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	1/49 (2)	2/50 (4)	4/50 (8)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.960	3.920
Lower Limit		0.106	0.407
Upper Limit		113.312	188.989
Weeks to First Observed Tumor	104	105	103
Hematopoietic System: Lymphomas or Leukemias[b]	20/49 (41)	11/50 (22)	14/50 (28)
P Values[c,d]	N.S.	P = 0.035(N)	N.S.
Relative Risk[f]		0.539	0.686
Lower Limit		0.264	0.366
Upper Limit		1.046	1.256
Weeks to First Observed Tumor	81	92	70

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcomas[b]	3/49 (6)	1/50 (2)	0/50 (0)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.327	0.000
Lower Limit		0.006	0.000
Upper Limit		3.903	1.629
Weeks to First Observed Tumor	102	50	--
Liver: Hepatocellular Carcinoma[b]	1/49 (2)	3/50 (6)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		2.940	2.940
Lower Limit		0.246	0.246
Upper Limit		151.180	151.180
Weeks to First Observed Tumor	104	105	105

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	3/33 (9)	4/40 (10)	2/33 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		1.100	0.667
Lower Limit		0.201	0.059
Upper Limit		7.050	5.439
Weeks to First Observed Tumor	104	105	105
Thyroid: Follicular-cell Adenoma[b]	3/43 (7)	0/41 (0)	0/44 (0)
P Values[c,d]	P = 0.037(N)	N.S.	N.S.
Relative Risk[f]		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.733	1.618
Weeks to First Observed Tumor	104	--	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Titanium Dioxide in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Adenocarcinoma, NOS[b]	1/49 (2)	1/50 (2)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.
Relative Risk[f]		0.980	2.940
Lower Limit		0.013	0.246
Upper Limit		75.404	151.180
Weeks to First Observed Tumor	104	105	90

[a]Dosed groups received 25,000 or 50,000 ppm.

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

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative, (N), indicates a lower incidence in a dosed group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF TITANIUM DIOXIDE

APPENDIX G

Analysis of Formulated Diets for Concentrations of Titanium Dioxide

Duplicate 100-mg subsamples of feed were ashed, and the residues fused with 2 g of potassium pyrosulfate. The fusion mixture was quantitatively transferred to a 100-ml volumetric flask using a 1:1 mixture of sulfuric acid and water, and diluted to volume with water. With a Tiron indicator, the transmittance of this solution was read at 410 nm. Concentrations of titanium dioxide were determined by comparison with standard solutions.

Recoveries were also determined from duplicate analyses of spiked samples worked up simultaneously with each set of dosed feed samples. The average recovery from the 2.5% spiked samples was 97.5%, and from the 5.0% spiked sample, 100.3%.

Theoretical Concentrations in Diet (% in diet)	No. of Samples	Sample Analytical Mean (% in diet)	Coefficient of Variation (%)	Range (% in diet)
2.5	10	2.4	26.3	2.2-2.9*
5.0	12	4.9	29.5	4.79-6.85*

*Ranges exclude the two samples at each level during weeks 35 and 45 which analyzed at only 40-50% of the theoretical; these samples were included in the Number of Samples, Sample Analytical Mean, and Coefficient of Variation.

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

August 31, 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 Titanium Dioxide for carcinogenicity.

The primary reviewer said that Titanium Dioxide did not significantly increase the incidence of tumors in treated mice, under the conditions of test. In treated high dose female rats, however, he noted an increased incidence in C-cell adenomas and carcinomas of the thyroid. Although the staff did not find the thyroid tumors to be statistically significant, the primary reviewer emphasized that the evidence was insufficient to conclude that Titanium Dioxide was not carcinogenic. He recommended that the report be accepted with the conclusion modified to indicate the equivocal findings in female rats. He suggested that the compound be considered for retest based on its wide human exposure and unclear findings in treated female rats.

The secondary reviewer agreed with the conclusion in the report that Titanium Dioxide was not carcinogenic, under the conditions of test. He considered the study to be adequate. He noted the increased incidence of C-cell adenomas and carcinomas of the thyroid in treated female rats, but did not consider it to be significant. Based on the results of the study, the secondary reviewer concluded that Titanium Dioxide would not appear to pose a carcinogenic risk to humans.

A Program staff member said that the incidence of C-cell tumors of the thyroid was not an unexpected finding in the Fischer rat. As a result, he found no evidence to contradict the conclusion that Titanium Dioxide was not carcinogenic under the conditions of test. He questioned whether a new study could be designed that would be a significant improvement over this bioassay.

As suggested wording for a revised conclusion, the primary reviewer proposed the following. "It was concluded that, under the conditions of this bioassay, Titanium Dioxide was not carcinogenic by the oral route of exposure for B6C3F1 mice, but that no firm conclusion can be reached about the possible carcinogenicity of this compound to Fischer 344 rats, at this time." There was no objection to the recommendation that the conclusion be modified as suggested. There also was no objection to the recommendation that Titanium Dioxide be considered for retest.

Members present were:

Arnold Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
(Kenneth Wilcox, Michigan State Health Department, submitted a written review)

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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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