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FOR POSSIBLE CARCINOGENICITY

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

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REPORT ON THE BIOASSAY OF ENDOSULFAN FOR POSSIBLE CARCINOGENICITY

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

FOREWORD: This report presents the results of the bioassay of endosulfan 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 environmental 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 the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

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

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

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

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6) and Dr. J. R. Joiner (7), using methods selected for the Bioassay Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), the task leader, Dr. M. R. Kornreich (6), the senior biologist, Ms. P. Walker (6), and the technical editor, Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (9), Mr. J. Nam (9), Dr. H. M. Pettigrew (9), and Dr. R. E. Tarone (9).

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

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1. Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia.

4. Now with the Center for Regulatory Services, 2347 Paddock Lane, Reston, Virginia.

5. Now with Rhodia, Inc., 23 Belmont Drive, Somerset, New Jersey.

6. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

7. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

8. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

9. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer

Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

10. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay of technical-grade endosulfan for possible carcinogenicity was conducted using Osborne-Mendel rats and B6C3F1 mice. Endosulfan was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species.

The time-weighted average high and low dietary concentrations of endosulfan were, respectively, 952 and 408 ppm for the male rats, and 445 and 223 ppm for the female rats. In mice the high and low time-weighted average concentrations were, respectively, 6.9 and 3.5 ppm for the males and 3.9 and 2.0 ppm for the females. Twenty animals of each sex and species were placed on test as controls. The bioassay of high dose male rats was terminated during week 82, and the bioassay of low dose male rats was terminated during week 74. After a 78-week period of chemical administration, observation of female rats continued for 33 additional weeks and observation of mice continued for 14 additional weeks.

At the doses administered to rats in this study endosulfan was toxic, inducing a high incidence of toxic nephropathy in both sexes and testicular atrophy in males.

In both species high early mortality was observed in the male groups and no conclusions concerning the carcinogenicity of endosulfan can be drawn from this part of the bioassay. However, survival among females of both species was sufficient for meaningful statistical evaluation of the incidence of late-developing tumors. It is concluded that under the conditions of this bioassay, technical-grade endosulfan was not carcinogenic in female Osborne-Mendel rats or in female B6C3F1 mice.

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I. INTRODUCTION

In the late 1960s scientists at the National Cancer Institute noted that a group of pesticides used extensively in agriculture had not been adequately tested for carcinogenicity. In 1969 the Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health further emphasized the need for chronic toxicity studies of certain specific pesticides (U.S. Department of Health, Education and Welfare, 1969). As a result, a chronic biossay of endosulfan* (NCI No. C00566), one of the chemicals included in this group, was conducted at Hazleton Laboratories America, Inc.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this pesticide is 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide. Endosulfan, a mixture of two geometric isomers, is a synthetic chlorinated cyclodiene and was introduced in 1956 as an experimental broad spectrum insecticide (Spencer, 1968). In 1971 farmers in the United States used roughly one million pounds of endosulfan (Andrelinas, 1974). About 20 percent of this quantity was used on Irish potatoes, with substantial application on other vegetables, tobacco, apples and other fruits, and nuts. By 1973, when endosulfan was registered for use on 59 agricultural crops, California alone used over 0.8 million pounds (Stanford Research Institute, 1974). Endosulfan residues in

*The CAS registry number is 115-29-7.

1973 averaged 0.001 ppm in potatoes, 0.019 ppm in leafy vegetables, and traces were found in a variety of fruits. Overall, endosulfan residues ranged from trace amounts to 0.439 ppm in over 8 percent of all food composites sampled during that year (Johnson and Manske, 1976).

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade endosulfan (Thiodan®) was purchased by Hazleton Laboratories America, Inc., Vienna, Virginia, from Niagara Chemical Division (now Agricultural Chemical Division of FMC Corporation). The manufacturer's analysis indicated a purity of 98.80 percent.

It should be noted that the presence of two geometric isomers (Thiodan I and Thiodan II) of the compound would tend to make it difficult to interpret results obtained by all but the most sophisticated analytical procedures. Gas-liquid chromatography (GLC) indicated two major peaks (presumed to represent the two isomers) comprising over 95 percent of the total area. Five minor peaks detected indicated the presence of at least five impurities. Similar results were obtained upon GLC analysis after one year.

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

B. Dietary Preparation

The basal laboratory diet for both control and dosed animals consisted of 2 percent Duke's® corn oil (S. F. Sauer Company) by weight added to Wayne Lab-Blox® meal (Allied Mills, Inc.). Fresh mixtures of endosulfan in corn oil were prepared each week and stored in the dark. The mixtures of endosulfan in corn oil were incorporated into the appropriate amount of the basal laboratory diet in a twin-shell blender fitted with an accelerator bar.

C. Animals

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

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

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle. The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors. Mice were housed by sex in groups of ten in solid-bottom

polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Shurfire) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles were provided three times a week. Food and water were available ad libitum.

The endosulfan-treated and control rats were housed in the same room with other rats receiving diets treated with* trifluralin (1582-09-8); dioxathion (78-34-2); dicofol (115-32-2); nitrofen (1836-75-5); and mexacarbate (315-18-4). All mice used in the endosulfan study were housed in the same room with other mice receiving diets treated with trifluralin (1582-09-8); dioxathion (78-34-2); sulfallate (95-06-7); p,p'-DDT (50-29-3); methoxychlor (72-43-5); p,p'-DDE (72-55-9); p,p'-TDE (72-54-8); dicofol (115-32-2); pentachloronitrobenzene (82-68-8); clonitralid (1420-04-8); nitrofen (1836-75-5); chlorobenzilate (510-15-6); mexacarbate (315-18-4); amitrole (61-82-5); acetylamino-fluorene (53-96-3); and safrole (94-59-7).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated doses of endosulfan for administration to treated animals in the chronic studies, sub-chronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each

*CAS registry numbers are given in parentheses.

consisting of five males and five females. Endosulfan was premixed with a small amount of corn oil. The mixture was then incorporated into the basal laboratory diet and fed ad libitum to five of the six rat groups at concentrations of 178, 316, 562, 1000, and 1780 ppm and five of the six mouse groups at concentrations of 3.2, 5.6, 10, 18, and 32 ppm. The sixth group of each species served as a control group, receiving only the basal laboratory diet. The dosed dietary preparations were administered for a period of 6 weeks, followed by a 2-week observation period during which all animals were fed the basal diet of corn oil and laboratory chow.

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

In the male rats a dose-related depression in mean group body weight was observed at concentrations of 562 ppm and above. At 562 and 1000 ppm, the mean group body weight depression was 9 and 20 percent, respectively. Three male rats died at 1780 ppm. In the female rats no dose-related depression in mean group body weight was observed, but one animal died at 316 ppm and four animals died at 562 ppm. The initial high concentrations selected for the chronic study were 562 ppm for the male rats and 178 ppm for the female rats.

In mice, depression in mean group body weight, although not clearly dose-related, was observed at concentrations of 5.6 ppm and

above. One male died at 10 ppm and one female died at 5.6 ppm. Mortality increased with concentration in both sexes. The initial high concentrations selected for the chronic study were 6 ppm for the male and 3 ppm for the female mice.

F. Experimental Design

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

At initiation of the study the treated and control rats were all approximately 7 weeks old. The concentrations of endosulfan initially utilized for males were 562 and 281 ppm. Throughout this report the male rats initially receiving the former concentration are referred to as the high dose group while the males initially receiving the latter concentration are referred to as the low dose group. In week 4, high and low concentrations were increased to 700 and 350 ppm, respectively; in week 11 the concentrations were increased to 900 and 450 ppm, and in week 21 the concentrations were raised to 1200 and 600 ppm. These increases in concentrations were made because of the animals' apparent tolerance of the chemical, but at the concentration of 1200 ppm, 13/50 male rats died. In week 44, administration of the compound was discontinued for 1 week, followed by 4 weeks of dosing. Cyclic administration at concentrations of 1200 and 600 ppm continued for a second 5-week cycle. In week 54 the high and low concentrations were reduced

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
ENDOSULFAN FEEDING EXPERIMENT

	INITIAL GROUP SIZE	ENDOSULFAN CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
MALE					
CONTROL	20	0		110	0
LOW DOSE[d]	50	281	3		408
		350	7		
		450	10		
		600	23		
		600[c]	8	2	
		450[c]	8	2	
		0		10	
		450[c]	4	1	
		0		3	
HIGH DOSE[e]	50	562	3		952
		700	7		
		900	10		
		1200	23		
		1200[c]	8	2	
		900[c]	8	2	
		0		10	
FEMALE					
CONTROL	20	0		110	0
LOW DOSE	50	89	3		223
		150	7		
		225	10		
		300	23		
		300[c]	8	2	
		225[c]	20	5	
		0		33	
HIGH DOSE	50	178	3		445
		300	7		
		450	10		
		600	23		
		600[c]	8	2	
		450[c]	20	5	
		0		33	

[a]Concentrations in parts per million.

[b]Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

[c]These concentrations were cyclically administered with a pattern of 1 dosage-free week followed by 4 weeks of dosing at the level indicated.

[d]These animals were sacrificed after 81 weeks.

[e]These animals were sacrificed after 73 weeks.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
ENDOSULFAN FEEDING EXPERIMENT

	INITIAL GROUP SIZE	ENDOSULFAN CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0		91	0
LOW DOSE	50	3.0	5		3.5
		3.5	73		
		0		14	
HIGH DOSE	50	6.0	5		6.9
		7.0	73		
		0		14	
FEMALE					
CONTROL	20	0		91	0
LOW DOSE	50	1.5	5		2
		2.0	73		
		0		14	
HIGH DOSE	50	3.0	5		3.9
		4.0	73		
		0		14	

[a]Concentrations in parts per million.

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

to 900 and 450 ppm, respectively, and the same method of cyclic administration was continued. Ten weeks later, dosing of both high and low dose male rats was discontinued and they received the basal diet only. During week 74 of the experiment the surviving high dose male rats were sacrificed. At this time the low dose males were again placed on the cyclic feeding schedule at a concentration of 450 ppm. In week 82 the surviving males in this group were sacrificed.

For female rats, the concentrations of endosulfan initially administered were 178 and 89 ppm. Throughout this report those female rats initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. In week 4 the high and low concentrations were increased to 300 and 150 ppm, respectively. In week 11 the concentrations were again increased, to 450 and 225 ppm, and in week 21 the concentrations were raised to 600 and 300 ppm. In week 44, 23 weeks after the last increase, administration of the compound was discontinued for 1 week, followed by 4 weeks of dosing. This cyclic administration, designed to decrease total compound intake due to apparent toxic effects of the chemical, continued for the remainder of the dosing period, but in week 54, the high and low concentrations were reduced to 450 and 225 ppm, respectively. Chemical administration to the female rats continued at these concentrations, on a cyclic basis, until week 78. They were

then observed for an additional 32 weeks before sacrifice at termination of the bioassay.

At initiation of the study the mice were all approximately 6 weeks old. The concentrations initially administered to the male mice were 6 and 3 ppm. Throughout this report those male mice initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. In week 6 of the experiment, the high and low concentrations were increased to 7 and 3.5 ppm, respectively. These concentrations were maintained for the remainder of the dosing period. Female mice received initial concentrations of 3 and 1.5 ppm. Throughout this report those female mice initially receiving the former concentration are referred to as the high dose group and those initially receiving the latter concentration are referred to as the low dose group. High and low concentrations were increased during week 6 to 4 and 2 ppm, respectively, and these levels were maintained until the end of the dosing period. After the 78-week dosing period, all groups were observed for 12 additional weeks.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected daily for mortality. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size,

and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. The presence of tissue masses was determined by observation and palpation of each animal.

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

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

Tissues for which slides were prepared were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized,

or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lessions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect

on survival used the method of Cox (1972) for testing two groups for equality and used Tarone's (1975) extensions of Cox's methods for testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality

(Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

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

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

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

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical

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

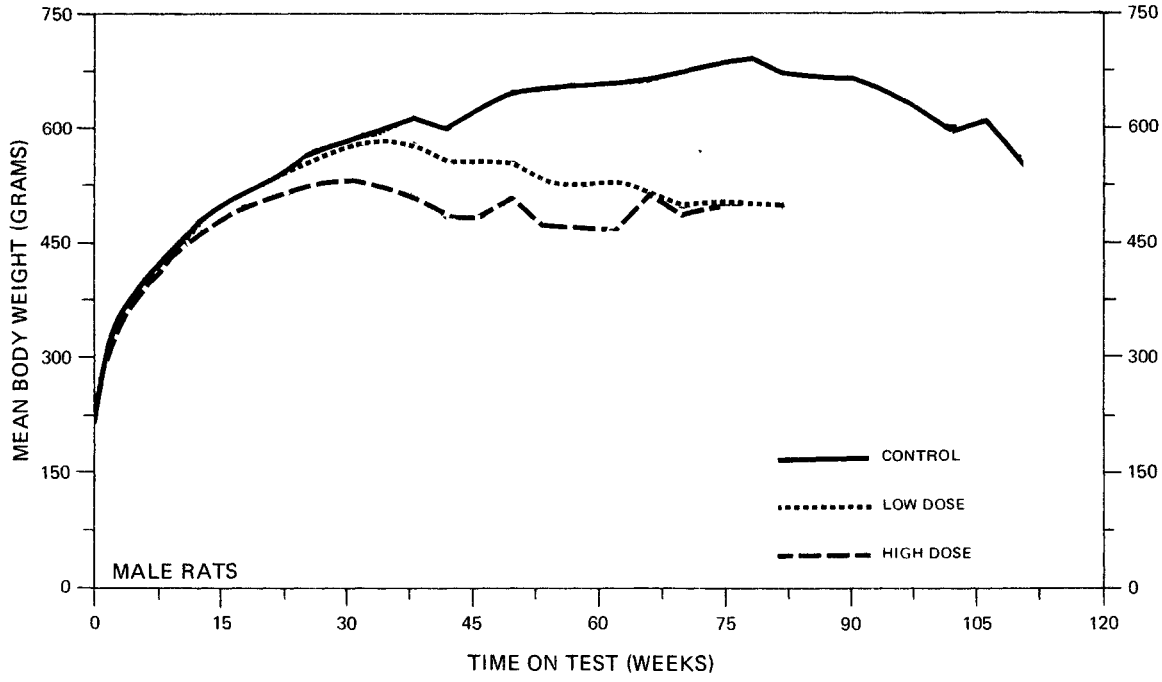
III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

No appreciable differences in mean body weight were observed among female rats (Figure 1). From week 35 to week 100, the high dose females did have a mean group body weight lower than the low dose and control groups, but at the end of the study all three female groups were similar in weight. A distinct dose-related depression in mean body weight was evident in males as early as week 22. The disparity between the treated and control males increased until weeks 74 and 82 when the high and low dose groups, respectively, were sacrificed. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

No other characteristic clinical signs were observed during the first 6 months of the study with the exception of occasional hunched appearance and reddened or squinted eyes in a few treated rats. As the study progressed, a hunched appearance was noted in increasing numbers of treated rats.

Other clinical signs included abdominal urine stains and rough fur. These signs were observed with a slightly greater frequency in the treated groups than in the control groups over the duration of the period of chemical administration but were noted at comparable rates in treated and control female rats during the observation period. Respiratory signs were observed at a low incidence in all



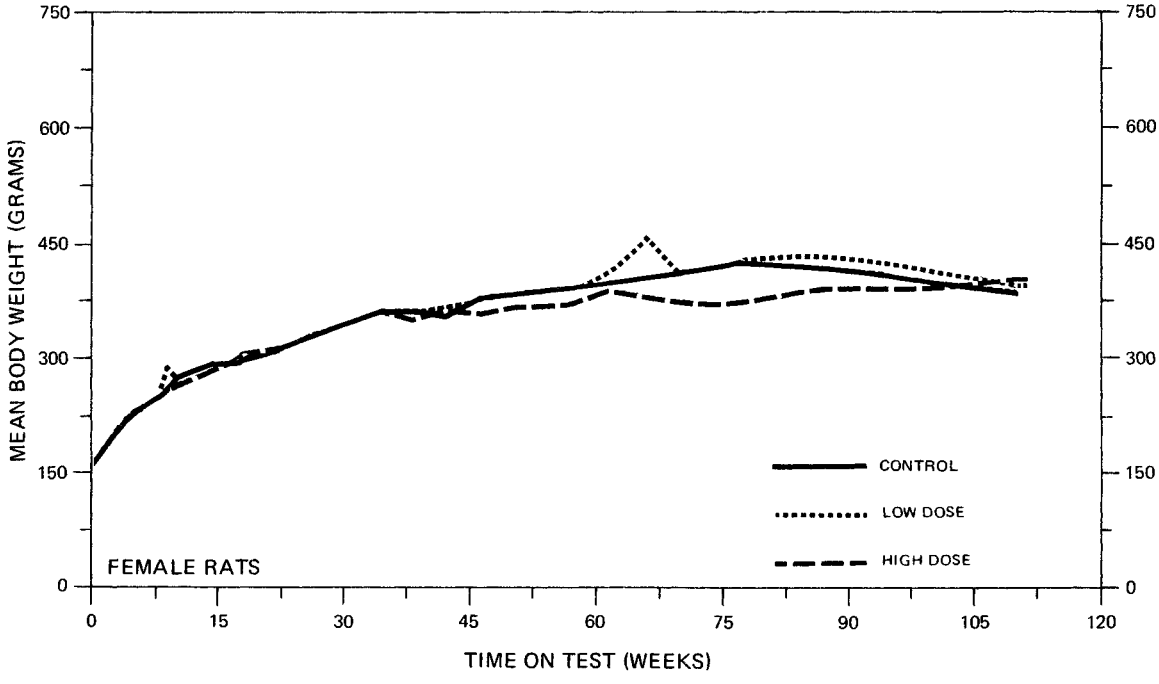


FIGURE 1
GROWTH CURVES FOR ENDOSULFAN CHRONIC STUDY RATS

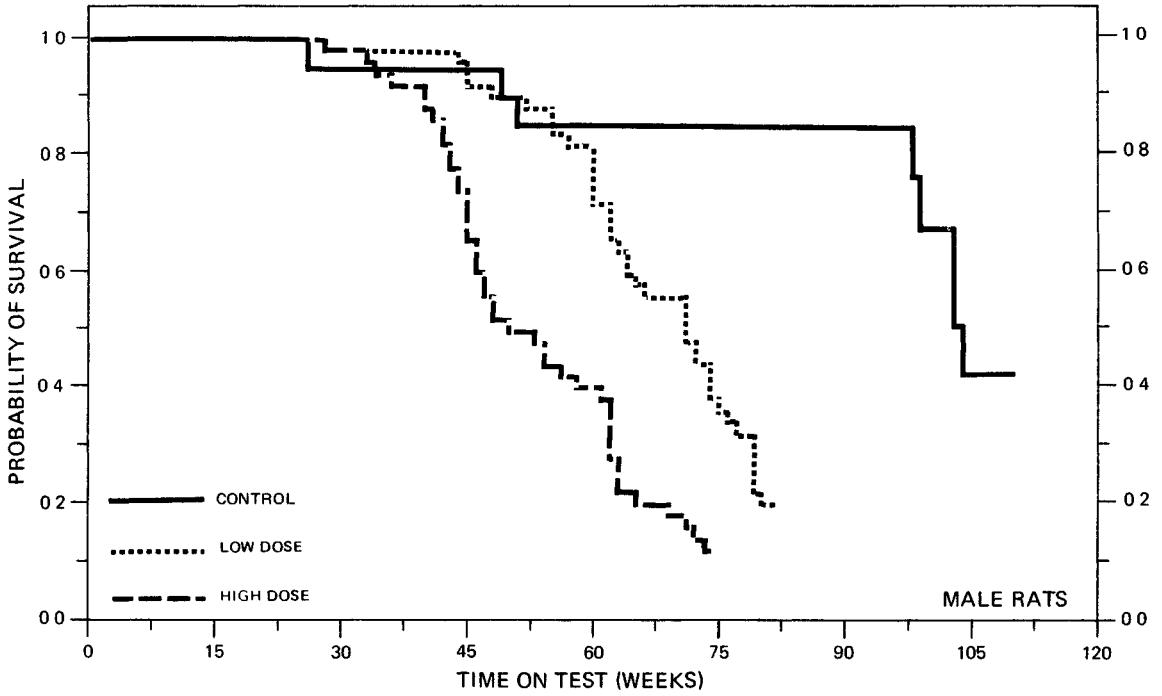
groups. Signs often associated with aging in group-housed laboratory rats were observed at a comparable rate in treated and control animals during the last 6 months of the study. These signs included alopecia, sores on the body and/or extremities, eye or nasal discharge, palpable nodules, tissue masses, and swollen areas. Isolated observations in one to three animals included head tilt, ataxia and circling.

B. Survival

The estimated probabilities of survival for male and female rats in the control and endosulfan-treated groups are shown in Figure 2.

For male rats the Tarone test for a positive dose-related trend in mortality was highly significant ($P < 0.001$). The usefulness of any analysis of late-developing tumors based upon the male rat data was restricted due to the early ages at which the animals died. By week 54, 52 percent of the high dose rats had died. The six high dose males surviving past week 71 were sacrificed in week 74. The 10 low dose males surviving past week 80 were sacrificed in week 82. Seven of the 17 surviving males in the control group were sacrificed in week 74; of the 10 male controls remaining 5 survived until termination of the study.

For female rats the Tarone test for a positive dose-related trend in mortality was not significant. The low dose group had a high early mortality, primarily due to the death of seven female rats in week 21. Six of these animals were reported to have cerebral hemorrhage and the seventh to have cerebral angiectasis; no other rats or mice included



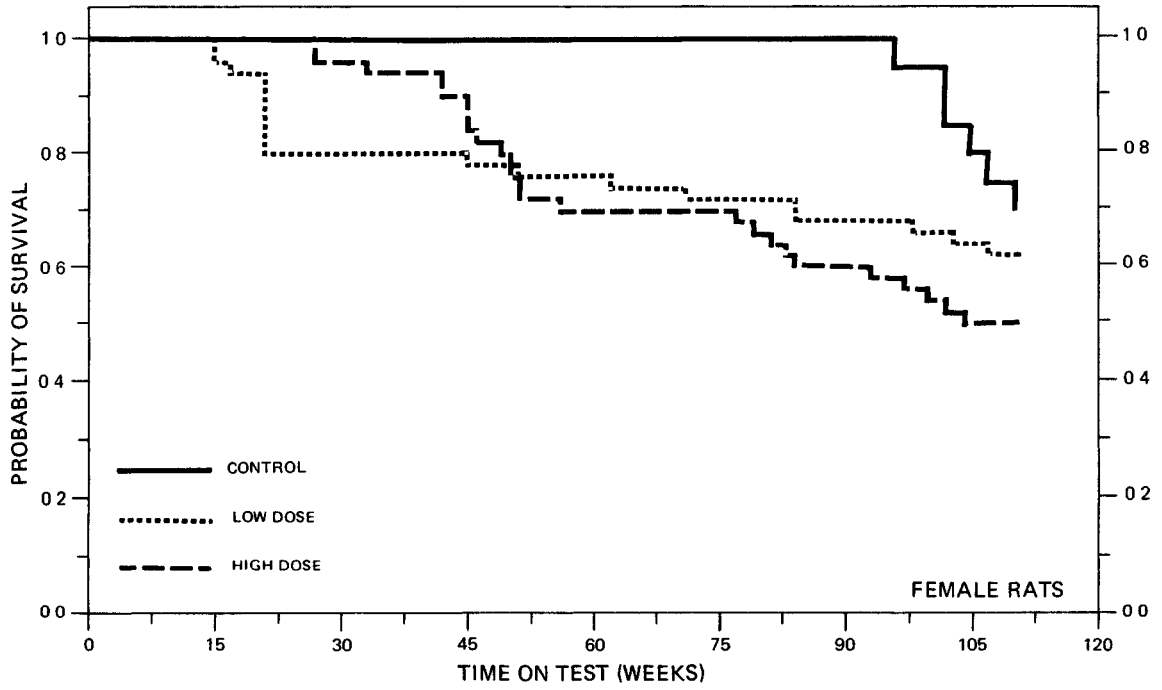


FIGURE 2
SURVIVAL COMPARISONS OF ENDOSULFAN CHRONIC STUDY RATS

in this bioassay in any control or endosulfan-treated groups were found to have cerebral lesions. These deaths do not appear, therefore, to be compound-related. Since 50 percent of the high dose animals, 62 percent of the low dose animals, and 70 percent of the controls survived to the termination of the study, adequate numbers of female rats survived sufficiently long to be at risk from late-developing tumors. Early deaths in the treated groups were not tumor-related.

C. Pathology

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

Toxic nephropathy occurred in 47/50 low dose males, 43/47 high dose males, 27/50 low dose females, and 29/50 high dose females. Microscopically, toxic nephropathy was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium. Some affected tubules were filled with hyalin casts. In occasional tubules, there were enlarged dark-staining regenerative tubular epithelial cells. At this stage the kidney often had infiltration of inflammatory cells, fibrosis, and focal mineralization. Parathyroid hyperplasia associated with renal lesions occurred in 21/48 low dose males, 18/47 high dose males, and 1/49 low dose females. Medial calcification of the blood vessels,

perhaps related to the hyperplasia of the parathyroid, occurred frequently in the treated male rats.

Testicular atrophy occurred in 3/19 control, 18/47 low dose, and 24/47 high dose male rats, and was characterized by degeneration and necrosis of the germinal cells lining the seminiferous tubules, multinucleated cells (fusion bodies), and calcium deposition resulting in aspermatogenesis.

Other inflammatory, degenerative, proliferative and neoplastic lesions in the control and treated animals were similar in number and kind to lesions that occur naturally in aged Osborne-Mendel rats.

In this study, endosulfan induced testicular atrophy in male rats and toxic nephropathy with secondary parathyroid hyperplasia in male and female rats. However, there was no histopathologic evidence of carcinogenicity.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or endosulfan-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to high early mortality, additional time-adjusted analyses were conducted for selected tumors in both males and females (Tables 5 and 6).

TABLE 3

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

TOPOGRAPHY: MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	2/40(0.05)	2/20(0.10)	2/50(0.04)	1/49(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.800	0.408
Lower Limit	---	---	0.060	0.007
Upper Limit	---	---	10.643	7.568
Relative Risk (Matched Control)[d]	---	---	0.400	0.204
Lower Limit	---	---	0.032	0.004
Upper Limit	---	---	5.277	3.754
Weeks to First Observed Tumor	49	49	28	40
Kidney: Mixed Tumor Malignant[b]	2/40(0.05)	2/20(0.10)	2/50(0.04)	0/47(0.00)
P Values[c]	N.S.	P = 0.044(N)	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.800	0.000
Lower Limit	---	---	0.060	0.000
Upper Limit	---	---	10.643	2.870
Relative Risk (Matched Control)[d]	---	---	0.400	0.000
Lower Limit	---	---	0.032	0.000
Upper Limit	---	---	5.282	1.428
Weeks to First Observed Tumor	110	110	82	---

TABLE 3 (Continued)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	6/39(0.15)	3/19(0.16)	1/49(0.02)	0/45(0.00)
P Values[c]	P = 0.003(N)	P = 0.010(N)	P = 0.028*(N)	P = 0.008*(N) P = 0.023**(N)
Relative Risk (Pooled Control)[d]	---	---	0.133	0.000
Lower Limit	---	---	0.003	0.000
Upper Limit	---	---	1.032	0.539
Relative Risk (Matched Control)[d]	---	---	0.129	0.000
Lower Limit	---	---	0.003	0.000
Upper Limit	---	---	1.517	0.694
Weeks to First Observed Tumor	96	98	63	---
Thyroid: Follicular-Cell Adenoma[b]	2/40(0.05)	1/20(0.05)	0/48(0.00)	0/47(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	2.812	2.871
Relative Risk (Matched Control)[d]	---	---	0.000	0.000
Lower Limit	---	---	0.000	0.000
Upper Limit	---	---	7.780	7.942
Weeks to First Observed Tumor	110	110	---	---

TABLE 3 (Concluded)

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[a]Treated groups received time-weighted average doses of 408 or 952 ppm in feed.

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

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

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

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	2/40(0.05)	1/20(0.05)	1/50(0.02)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.400	0.000
Lower Limit	---	---	0.007	0.000
Upper Limit	---	---	7.421	2.702
Relative Risk (Matched Control)[d]	---	---	0.400	0.000
Lower Limit	---	---	0.005	0.000
Upper Limit	---	---	30.802	7.475
Weeks to First Observed Tumor	55	110	111	---
Subcutaneous Tissue: Fibrosarcoma[b]	2/40(0.05)	2/20(0.10)	1/50(0.02)	0/50(0.00)
P Values[c]	N.S.	P = 0.035(N)	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.400	0.000
Lower Limit	---	---	0.007	0.000
Upper Limit	---	---	7.421	2.702
Relative Risk (Matched Control)[d]	---	---	0.200	0.000
Lower Limit	---	---	0.004	0.000
Upper Limit	---	---	3.682	1.345
Weeks to First Observed Tumor	110	110	111	---

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	20/39(0.51)	11/19(0.58)	16/48(0.33)	9/48(0.19)
P Values[c]	P = 0.001(N)	P = 0.002(N)	N.S.	P = 0.001*(N) P = 0.003**(N)
Relative Risk (Pooled Control)[d]	---	---	0.650	0.366
Lower Limit	---	---	0.376	0.172
Upper Limit	---	---	1.132	0.735
Relative Risk (Matched Control)[d]	---	---	0.576	0.324
Lower Limit	---	---	0.337	0.159
Upper Limit	---	---	1.138	0.725
Weeks to First Observed Tumor	79	102	84	100
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	2/39(0.05)	2/19(0.11)	1/48(0.02)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.406	0.406
Lower Limit	---	---	0.007	0.007
Upper Limit	---	---	7.526	7.526
Relative Risk (Matched Control)[d]	---	---	0.198	0.198
Lower Limit	---	---	0.004	0.004
Upper Limit	---	---	3.635	3.635
Weeks to First Observed Tumor	110	110	98	111

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma NOS[b]	2/40(0.05)	2/20(0.10)	3/50(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	1.200	0.400
Lower Limit	---	---	0.145	0.007
Upper Limit	---	---	13.831	7.419
Relative Risk (Matched Control)[d]	---	---	0.600	0.200
Lower Limit	---	---	0.076	0.004
Upper Limit	---	---	6.860	3.682
Weeks to First Observed Tumor	110	110	111	111
Mammary Gland: Fibroadenoma[b]	10/40(0.25)	5/20(0.25)	13/50(0.26)	11/50(0.22)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	1.040	0.880
Lower Limit	---	---	0.475	0.381
Upper Limit	---	---	2.376	2.082
Relative Risk (Matched Control)[d]	---	---	1.040	0.880
Lower Limit	---	---	0.416	0.336
Upper Limit	---	---	3.342	2.905
Weeks to First Observed Tumor	109	110	98	97

TABLE 4 (Continued)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	2/40(0.05)	1/20(0.05)	3/49(0.06)	1/49(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	1.224	0.408
Lower Limit	---	---	0.148	0.007
Upper Limit	---	---	14.113	7.568
Relative Risk (Matched Control)[d]	---	---	1.224	0.408
Lower Limit	---	---	0.108	0.005
Upper Limit	---	---	62.958	31.414
Weeks to First Observed Tumor	110	110	110	111
Hematopoietic System: Malignant Lymphoma[b]	0/40(0.00)	0/20(0.00)	3/50(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.019	P = 0.047	---	---
Relative Risk (Pooled Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.485	---
Upper Limit	---	---	Infinite	---
Relative Risk (Matched Control)[d]	---	---	Infinite	---
Lower Limit	---	---	0.250	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	71	---

TABLE 4 (Concluded)

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[a]Treated groups received time-weighted average doses of 223 or 446 ppm in feed.

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

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

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

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH ENDOSULFAN WHICH SURVIVED AT LEAST 52 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	6/36(0.17)	3/16(0.19)	1/44(0.02)	0/24(0.00)
P Values[c]	P = 0.010(N)	P = 0.020(N)	P = 0.030(N)	P = 0.039(N)
Relative Risk (Pooled Control)[d]	---	---	0.136	0.000
Lower Limit	---	---	0.003	0.000
Upper Limit	---	---	1.053	0.908
Relative Risk (Matched Control)[d]	---	---	0.121	0.000
Lower Limit	---	---	0.002	0.000
Upper Limit	---	---	1.409	1.066
Weeks to First Observed Tumor	---	98	63	---
Kidney: Mixed Tumor, Malignant[b]	2/37(0.05)	2/17(0.12)	2/45(0.04)	0/24(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.822	0.000
Lower Limit	---	---	0.062	0.000
Upper Limit	---	---	10.895	5.073
Relative Risk (Matched Control)[d]	---	---	0.378	0.000
Lower Limit	---	---	0.030	0.000
Upper Limit	---	---	4.953	2.319
Weeks to First Observed Tumor	110	110	82	---

TABLE 5 (Concluded)

[a]Treated groups received time-weighted average doses of 408 or 952 ppm in feed.

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

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

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

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH ENDOSULFAN WHICH SURVIVED AT LEAST 52 WEEKS[a]

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	2/39(0.05)	2/20(0.10)	1/38(0.03)	0/36(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.513	0.000
Lower Limit	---	---	0.009	0.000
Upper Limit	---	---	9.434	3.625
Relative Risk (Matched Control)[d]	---	---	0.263	0.000
Lower Limit	---	---	0.005	0.000
Upper Limit	---	---	4.801	1.852
Weeks to First Observed Tumor	110	110	111	---
Pituitary: Chromophobe Adenoma[b]	20/38(0.53)	11/19(0.58)	16/36(0.44)	9/34(0.26)
P Values[c]	P = 0.018(N)	P = 0.015(N)	N.S.	P = 0.025(N) P = 0.021(N)
Relative Risk (Pooled Control)[d]	---	---	0.844	0.503
Lower Limit	---	---	0.498	0.240
Upper Limit	---	---	1.418	0.980
Relative Risk (Matched Control)[d]	---	---	0.768	0.457
Lower Limit	---	---	0.452	0.225
Upper Limit	---	---	1.472	0.999
Weeks to First Observed Tumor	79	102	84	100

TABLE 6 (Concluded)

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[a]Treated groups received time-weighted average doses of 223 or 445 ppm in feed.

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

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

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

In addition to the control group specifically assigned in the experimental design to the endosulfan bioassay (referred to in this section as the "matched" control), a pooled control group was used for statistical purposes. The pooled group combined the controls from the studies of endosulfan and mexacarbate. All of these control rats were of the same strain, were housed in the same room, were tested at approximately the same time, and were examined by the same pathologists.

For both male and female rats, neither the Cochran-Armitage tests nor the Fisher exact tests indicated a significant positive association between dosage and tumor incidence at the 0.05 level for any type of tumor. For male rats the incidence of neoplasms was almost uniformly higher in the matched control group than in the high and low dose groups. This was probably due to the absence of dosed animals surviving long enough for late-developing tumors to occur.

For both male and female rats all Cochran-Armitage tests indicated a significant negative association between dosage and the incidence of pituitary chromophobe adenomas. For males, however, the time-adjusted Fisher exact tests did not support this finding since the marginal results were not significant under the Bonferroni criterion. For females the time-adjusted Fisher exact tests indicated that the high dose incidence was significantly lower than either the pooled ($P = 0.025$) or the matched ($P = 0.021$) control. It must be noted, however, that the incidence in the controls was somewhat higher

than the 40/160 (25 percent) observed in the historical Osborne-Mendel untreated control females maintained at Hazleton Laboratories for the NCI Bioassay Program.

For malignant mixed tumors of the kidney in males and for fibrosarcomas of the subcutaneous tissue in females, the Cochran-Armitage test indicated a significant negative association between dosage and incidence. In both cases, however, no Fisher exact tests were significant.

To provide additional insight into the statistical implications of the biological findings, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3, 4, 5, and 6, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by endosulfan that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

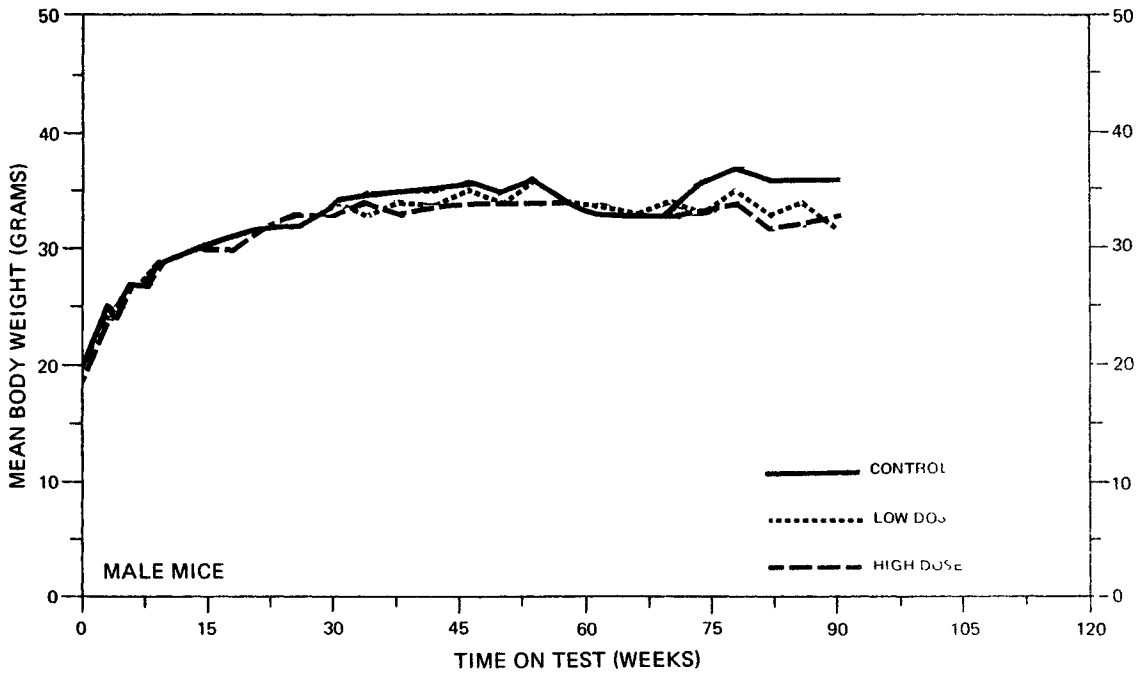
A. Body Weights and Clinical Observations

No appreciable differences in mean body weight were observed among the control and endosulfan-treated female mice (Figure 3). The same held true for the male mice until after week 73, where the curve indicates a gain in body weight for control males, while weights for both of the treated groups remained approximately the same. Since mice do not normally gain body weight at that age, the increase in weight of male controls is apparently an artifact, indicating that the 5 male controls surviving beyond week 73 were heavier than the 11 male controls that died in that week. Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

There were no definite compound-related effects on appearance and behavior in any of the treated groups during the study. Signs often observed in group-housed laboratory mice of this hybrid strain were observed at a similar frequency in treated and control groups throughout the study. These signs included sores on the body (particularly in males), alopecia, hunched appearance, penile, anal, or vulvar irritation, rough fur, bloated appearance, and palpable nodules or tissue masses.

B. Survival

The estimated probabilities of survival for male and female mice in the control and endosulfan-treated groups are shown in Figure 4.



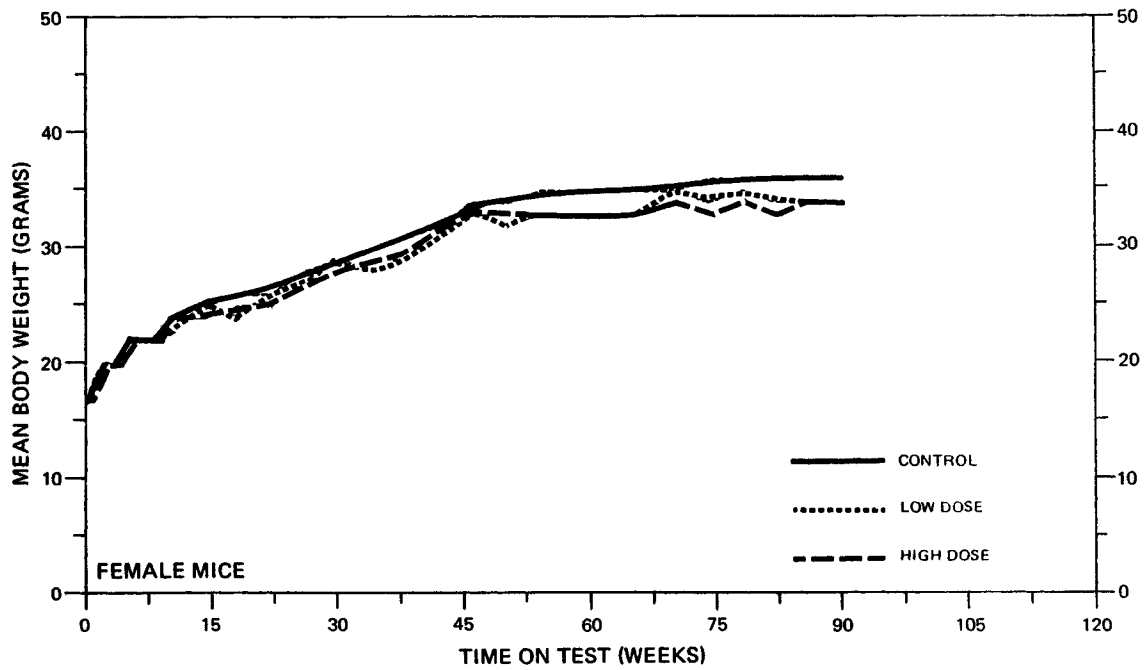
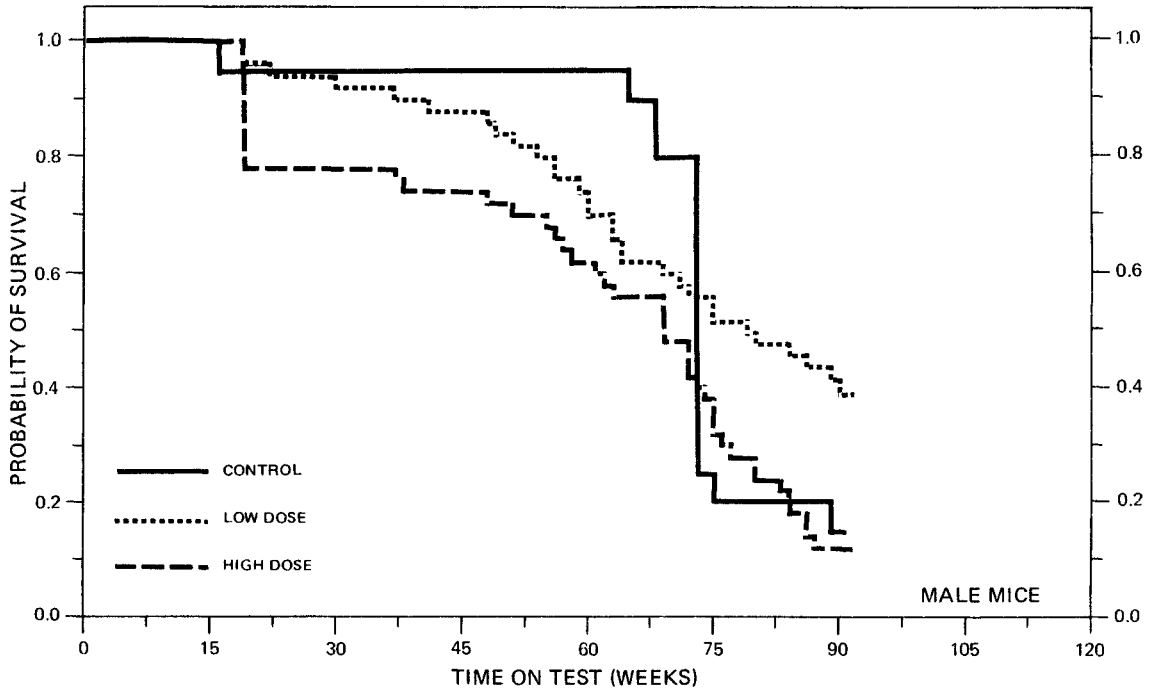


FIGURE 3
GROWTH CURVES FOR ENDOSULFAN CHRONIC STUDY MICE



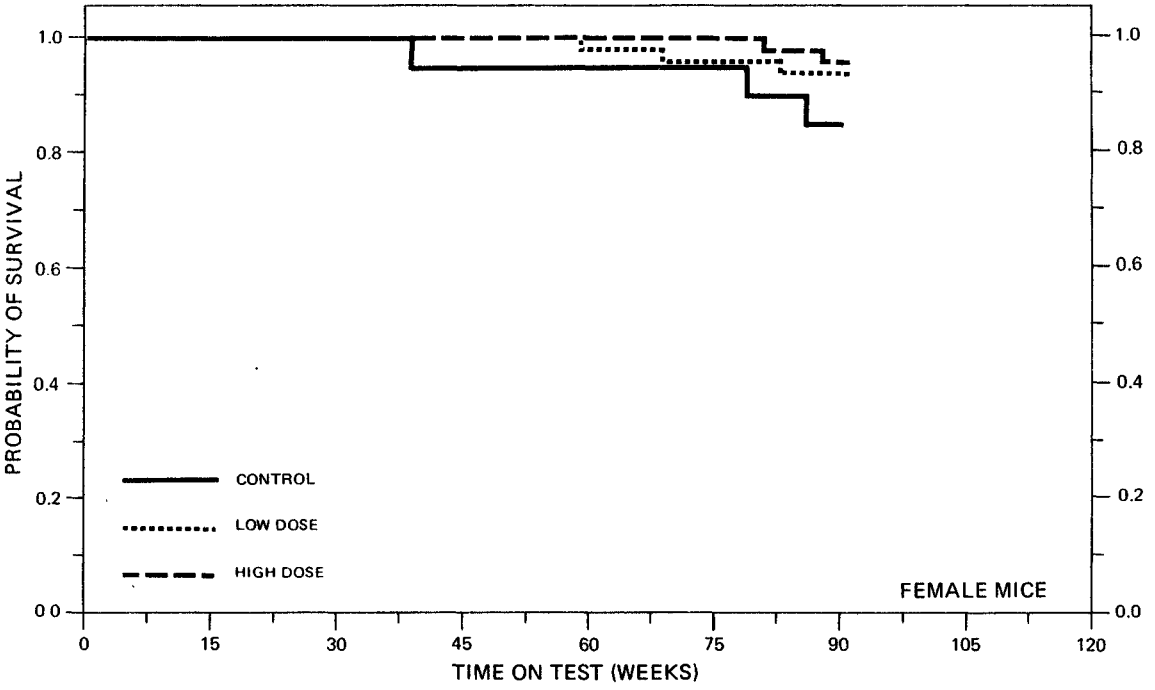


FIGURE 4
SURVIVAL COMPARISONS OF ENDOSULFAN CHRONIC STUDY MICE

Although high mortality was noted in male mice, the Tarone test for association between increased dosage and elevated mortality was not significant. The meaning of these results is difficult to interpret because of the deaths of 11 high dose males in week 19 and of 11 control males in week 73. There is an indication that the deaths in the control group may have been due to fighting among the animals. No common cause of death was found for the high dose males. Ten percent of the high dose, 38 percent of the low dose, and 15 percent of the control group lived to the end of the test. Early deaths in the males were not tumor-related.

In female mice the Tarone test did not indicate a significant association between increased dosage and elevated mortality. Survival of the female mice was extremely good with 96 percent of the high dose, 94 percent of the low dose, and 85 percent of the controls living to termination of the bioassay. Thus, adequate numbers of females survived sufficiently long to be at risk from late-developing tumors.

C. Pathology

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

Hepatocellular carcinomas occurred in 1/20 (5 percent) control males, 6/49 (12 percent) low dose males, 2/50 (4 percent) high dose males, and 1/50 (2 percent) high dose females. Osteosarcomas occurred in one high dose male and one low dose female.

Inflammatory, degenerative, proliferative, and other neoplastic lesions as seen in the control and treated animals were similar in number and kind to lesions occurring naturally in aged B6C3F1 mice.

This histopathologic examination provided no evidence for the carcinogenicity of endosulfan in B6C3F1 mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 7 and 8. The analysis is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or endosulfan-dosed groups and where such tumors were observed in at least 5 percent of the group.

In addition to the control group specifically assigned in the experimental design to the endosulfan bioassay (referred to in this section as the "matched" control), a pooled control group was used for statistical purposes. This pooled group combined the controls from the studies of endosulfan and mexacarbate. All of these control mice were of the same strain, were housed in the same room, were tested at approximately the same time, and were examined by the same pathologists.

For both male and female mice, neither the Cochran-Armitage tests nor the Fisher exact tests indicated a significant positive association between dosage and tumor incidence at the 0.05 level for any type of tumor. Because of the extreme early mortality in male

TABLE 7

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

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	3/35(0.09)	3/20(0.15)	1/49(0.02)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.238	0.467
Lower Limit	---	---	0.005	0.041
Upper Limit	---	---	2.832	3.879
Relative Risk (Matched Control)[d]	---	---	0.136	0.267
Lower Limit	---	---	0.003	0.024
Upper Limit	---	---	1.599	2.191
Weeks to First Observed Tumor	73	73	92	86
Liver: Hepatocellular Carcinoma[b]	1/35(0.03)	1/20(0.05)	6/49(0.12)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	4.286	1.400
Lower Limit	---	---	0.557	0.076
Upper Limit	---	---	192.714	80.948
Relative Risk (Matched Control)[d]	---	---	2.440	0.800
Lower Limit	---	---	0.332	0.045
Upper Limit	---	---	110.166	46.273
Weeks to First Observed Tumor	73	73	92	75

TABLE 7 (Concluded)

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[a]Treated groups received time-weighted average doses of 3.5 or 6.9 ppm in feed.

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

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

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

TABLE 8

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

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/40(0.03)	1/20(0.05)	1/50(0.02)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.800	0.000
Lower Limit	---	---	0.011	0.000
Upper Limit	---	---	61.572	14.930
Relative Risk (Matched Control)[d]	---	---	0.400	0.000
Lower Limit	---	---	0.005	0.000
Upper Limit	---	---	30.802	7.475
Weeks to First Observed Tumor	91	91	92	---
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	3/40(0.08)	2/20(0.10)	5/50(0.10)	0/50(0.00)
P Values[c]	N.S.	P = 0.040(N)	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	1.333	0.000
Lower Limit	---	---	0.278	0.000
Upper Limit	---	---	8.155	1.328
Relative Risk (Matched Control)[d]	---	---	1.000	0.000
Lower Limit	---	---	0.184	0.000
Upper Limit	---	---	10.007	1.345
Weeks to First Observed Tumor	87	91	92	---

TABLE 8 (Concluded)

TOPOGRAPHY:MORPHOLOGY	POOLED CONTROL	MATCHED CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	9/40(0.22)	5/20(0.25)	10/50(0.20)	5/50(0.10)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[d]	---	---	0.889	0.444
Lower Limit	---	---	0.362	0.127
Upper Limit	---	---	2.241	1.356
Relative Risk (Matched Control)[d]	---	---	0.800	0.400
Lower Limit	---	---	0.296	0.107
Upper Limit	---	---	2.690	1.584
Weeks to First Observed Tumor	39	39	83	40

[a]Treated groups received time-weighted average doses of 2.0 or 3.9 ppm in feed.

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

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

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

mice, a time-adjusted analysis was performed in which animals that died before 52 weeks of study were eliminated; again no statistically significant positive results were observed. This bioassay, therefore, provided no statistical evidence for the carcinogenicity of endosulfan in B6C3F1 mice.

For female mice the Cochran-Armitage test indicated a significant (P = 0.040) negative association between administration and the incidence of alveolar/bronchiolar neoplasms. The Fisher exact tests, however, were not significant.

To provide additional insight into the statistical implications of the biological findings, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 7 and 8, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by endosulfan that could not be established under the conditions of this test.

V. DISCUSSION

In rats high early mortality, associated with toxic nephropathy, occurred in both treated male groups. The six high dose males surviving past week 71 were sacrificed in week 74. The 10 low dose males surviving past week 80 were sacrificed in week 82. Probably as a result of the low survival rate, the incidence of neoplasms was almost uniformly higher in the control group than in the high and low dose groups. Survival of female rats was considered sufficient for statistical analysis of late-appearing tumors.

At the doses fed to rats in this study, endosulfan was toxic, inducing a high incidence of toxic nephropathy in both sexes and testicular atrophy in males. The poor survival in male rats was associated with secondary parathyroid hyperplasia and mineralization (calcium deposits) in several tissues, both lesions resulting from the effects of chronic renal failure.

High early mortality was observed among male mice. Eleven high dose males and two low dose males died in week 19. Median survival on test was 69 weeks for high dose males, 75 weeks for low dose males, and 73 weeks for control males. Survival at termination of the bioassay was 10 percent (5/50) in the high dose males, 39 percent (19/50) in the low dose males, and 15 percent (3/20) in the control group males. Among the female mice, survival in all groups was high, providing sufficient animals for statistical analysis of late-appearing tumors. No significant increases in tumor incidence were observed

among dosed mice of either sex. The toxic nephropathy observed in both sexes of rats and the testicular atrophy observed in male rats were not seen in mice.

No conclusions concerning the carcinogenicity of endosulfan can be drawn from the bioassay of male rats or male mice because of the abbreviated life spans of these animals. However, survival among females of both species was sufficient for meaningful statistical evaluation of the incidence of late-developing tumors. It is concluded that under the conditions of this bioassay, technical-grade endosulfan was not carcinogenic in female Osborne-Mendel rats or in female B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH ENDOSULFAN

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

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	47
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(49)
SEBACEOUS ADENOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(47)
FIBROSARCOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (10%)	1 (2%)	
LYMPHOCYTIC LEUKEMIA	1 (5%)		
*SUBCUT TISSUE/AXILLA	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#SPLEEN	(20)	(49)	(46)
HEMANGIOSARCOMA	1 (5%)		
#CERVICAL LYMPH NODE	(20)	(41)	(40)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(20)	(50)	(47)
SARCOMA, NOS		1 (2%)	
DIGESTIVE SYSTEM			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(47)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	1 (2%)
MIXED TUMOR, MALIGNANT	2 (10%)	2 (4%)	
HEMANGIOSARCOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(49)	(45)
CHROMOPHOBE ADENOMA	3 (16%)	1 (2%)	
#THYROID	(20)	(48)	(47)
FOLLICULAR-CELL ADENOMA	1 (5%)		
#PANCREATIC ISLETS	(20)	(50)	(47)
ISLET-CELL ADENOMA	3 (15%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(49)
FIBROADENOMA		1 (2%)	
#PROSTATE	(13)	(29)	(19)
LIPOMA		1 (3%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF BACK	(20)	(50)	(49)
FIBROSARCOMA	1 (5%)		
BODY CAVITIES			
NONE			

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

TABLE A1 (CONCLUDED)

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	7	40	44
MORIBUND SACRIFICE	1		
SCHEDULED SACRIFICE	7		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	5	10	6
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	8	3
TOTAL PRIMARY TUMORS	14	10	3
TOTAL ANIMALS WITH BENIGN TUMORS	6	4	
TOTAL BENIGN TUMORS	7	4	
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	6	3
TOTAL MALIGNANT TUMORS	7	6	3
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH ENDOSULFAN

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA	1 (5%)	1 (2%)	
FIBROSARCOMA	2 (10%)	1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
MIXED TUMOR, METASTATIC		1 (2%)	
HEMANGIOSARCOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
#SPLEEN	(20)	(50)	(50)
HEMANGIOSARCOMA	1 (5%)		1 (2%)
#CERVICAL LYMPH NODE	(20)	(48)	(40)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
HEPATOCELLULAR CARCINOMA		1 (2%)	1 (2%)
#PANCREAS	(20)	(50)	(48)
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMANGIOSARCOMA, METASTATIC	1 (5%)		

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

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
#LARGE INTESTINE	(20)	(50)	(47)
FIBROSARCOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
TUBULAR-CELL ADENOMA			1 (2%)
LIPOSARCOMA			1 (2%)
MIXED TUMOR, MALIGNANT	1 (5%)	2 (4%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(48)	(48)
CHROMOPHOBE ADENOMA	11 (58%)	16 (33%)	9 (19%)
#ADRENAL	(20)	(50)	(50)
CORTICAL ADENOMA		2 (4%)	
#THYROID	(19)	(48)	(48)
FOLLICULAR-CELL ADENOMA	2 (11%)		
FOLLICULAR-CELL CARCINOMA		1 (2%)	1 (2%)
C-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCARCINOMA, NOS	2 (10%)	3 (6%)	1 (2%)
FIBROADENOMA	5 (25%)	13 (26%)	11 (22%)
*VAGINA	(20)	(50)	(50)
LEIOMYOMA			1 (2%)
#UTERUS	(20)	(49)	(49)
LIPOMA	1 (5%)		
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (5%)	3 (6%)	1 (2%)
#OVARY	(20)	(50)	(50)
GRANULOSA-CELL TUMOR		1 (2%)	
LIPOMA	1 (5%)		
LEIOMYOSARCOMA, METASTATIC		1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
ASTROCYTOMA		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	6	19	25
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	31	25
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	15	30	24
TOTAL PRIMARY TUMORS	28	50	32
TOTAL ANIMALS WITH BENIGN TUMORS	14	23	19
TOTAL BENIGN TUMORS	22	35	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	12	7
TOTAL MALIGNANT TUMORS	6	14	8
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	3	
TOTAL SECONDARY TUMORS	1	3	
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 TREATED WITH ENDOSULFAN

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH ENDOSULFAN

	CONTROL (VEH) 02-M072	LOW DOSE 02-M073	HIGH DOSE 02-M074
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
FIBROMA			1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)
*SUBCUT TISSUE	(20)	(49)	(50)
FIBROSARCOMA	3 (15%)	1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
NONE			
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEPATOCELLULAR CARCINOMA	1 (5%)	6 (12%)	2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			

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

TABLE B1 (CONTINUED)

	CONTROL(VEH) 02-M072	LOW DOSE 02-M073	HIGH DOSE 02-M074
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
ADENOCARCINOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE/LOWER EXTREMITY	(20)	(49)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	17	30	45
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	3	19	5
ANIMAL MISSING		1	

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 02-M072	LOW DOSE 02-M073	HIGH DOSE 02-M074
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	4	8	7
TOTAL PRIMARY TUMORS	4	9	9
TOTAL ANIMALS WITH BENIGN TUMORS		1	3
TOTAL BENIGN TUMORS		1	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	7	5
TOTAL MALIGNANT TUMORS	4	8	6
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (VEH) 02-F072	LOW DOSE 02-F075	HIGH DOSE 02-F076
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROSARCOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	4 (8%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	1 (2%)	
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (10%)	6 (12%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (15%)		
#SPLEEN	(20)	(50)	(50)
HEMANGIOSARCOMA	1 (5%)		1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)
#MESENTERIC L. NODE	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#LIVER	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#SMALL INTESTINE	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-F072	LOW DOSE 02-F075	HIGH DOSE 02-F076
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
HEPATOCELLULAR CARCINOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(44)	(50)
CHROMOPHOBE ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
#UTERUS	(20)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
#UTERUS/ENDOMETRIUM	(20)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)		
#OVARY	(20)	(49)	(50)
GRANULOSA-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*FEMUR	(20)	(50)	(50)
OSTEOSARCOMA		1 (2%)	

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

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 02-F072	LOW DOSE 02-F075	HIGH DOSE 02-F076
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	3	3	2
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	47	48
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	7	18	8
TOTAL PRIMARY TUMORS	9	19	11
TOTAL ANIMALS WITH BENIGN TUMORS	1	4	1
TOTAL BENIGN TUMORS	1	4	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	14	6
TOTAL MALIGNANT TUMORS	8	15	9
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

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

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH ENDOSULFAN

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	47
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(49)
ABSCESS, NOS	1 (5%)		
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(48)	(47)
INFLAMMATION, NOS			1 (2%)
#LUNG	(20)	(50)	(47)
PNEUMONIA, CHRONIC MURINE	11 (55%)	7 (14%)	17 (36%)
CALCIUM DEPOSIT		11 (22%)	5 (11%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(20)	(48)	(47)
METAMORPHOSIS FATTY	1 (5%)		
#SPLEEN	(20)	(49)	(46)
THROMBUS, ORGANIZED			1 (2%)
ABSCESS, NOS			1 (2%)
HEMATOPOIESIS	3 (15%)	2 (4%)	
#CERVICAL LYMPH NODE	(20)	(41)	(40)
INFLAMMATION, NOS	2 (10%)		
#THYMUS	(13)	(31)	(20)
INFLAMMATION, NOS	1 (8%)		
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(47)
CALCIUM DEPOSIT	1 (5%)	9 (18%)	10 (21%)
CALCIFICATION, NOS			1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
#MYOCARDIUM	(20)	(50)	(47)
INFLAMMATION, NOS	1 (5%)		
FIBROSIS		3 (6%)	2 (4%)
DEGENERATION, NOS		2 (4%)	2 (4%)
*AORTA	(20)	(50)	(49)
MEDIAL CALCIFICATION	1 (5%)	29 (58%)	22 (45%)
*CORONARY ARTERY	(20)	(50)	(49)
MEDIAL CALCIFICATION		1 (2%)	
*MESENTERIC ARTERY	(20)	(50)	(49)
THROMBUS, ORGANIZED			1 (2%)
MEDIAL CALCIFICATION	1 (5%)	28 (56%)	23 (47%)
*SPERMATIC ARTERY	(20)	(50)	(49)
MEDIAL CALCIFICATION		6 (12%)	4 (8%)
*PROSTATIC ARTERY	(20)	(50)	(49)
MEDIAL CALCIFICATION		2 (4%)	2 (4%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(47)
INFLAMMATION, NOS			1 (2%)
ABSCESS, NOS			3 (6%)
PELIOSIS HEPATIS	1 (5%)	1 (2%)	1 (2%)
METAMORPHOSIS FATTY	3 (16%)	15 (31%)	7 (15%)
CALCIUM DEPOSIT			1 (2%)
ANGIECTASIS	1 (5%)	2 (4%)	2 (4%)
*BILE DUCT	(20)	(50)	(49)
HYPERPLASIA, NOS	2 (10%)	4 (8%)	2 (4%)
#PANCREAS	(20)	(50)	(47)
PERIARTERITIS		2 (4%)	1 (2%)
#STOMACH	(20)	(50)	(47)
INFLAMMATION, NOS		1 (2%)	
CALCIUM DEPOSIT	1 (5%)	31 (62%)	21 (45%)
CALCIFICATION, NOS			1 (2%)
#COLON	(20)	(50)	(43)
NEMATODIASIS		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(47)
HYDRONEPHROSIS		1 (2%)	1 (2%)
PYELONEPHRITIS, NOS	1 (5%)		
INFLAMMATION, CHRONIC	8 (40%)	42 (84%)	34 (72%)
NEPHROPATHY, TOXIC		47 (94%)	43 (91%)
CALCIUM DEPOSIT	1 (5%)	29 (58%)	22 (47%)
CALCIFICATION, NOS		1 (2%)	
PIGMENTATION, NOS			2 (4%)
#URINARY BLADDER	(20)	(49)	(47)
CALCIUM DEPOSIT		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(49)	(45)
CYST, NOS		1 (2%)	
#ADRENAL	(20)	(50)	(47)
ANGIECTASIS	1 (5%)		
#THYROID	(20)	(48)	(47)
FOLLICULAR CYST, NOS	6 (30%)		2 (4%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)
#PARATHYROID	(19)	(48)	(47)
HYPERPLASIA, NOS		21 (44%)	18 (38%)
REPRODUCTIVE SYSTEM			
*PENIS	(20)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
#PROSTATE	(13)	(29)	(19)
INFLAMMATION, NOS			1 (5%)
CALCIUM DEPOSIT		1 (3%)	
#TESTIS	(19)	(47)	(47)
CALCIUM DEPOSIT		5 (11%)	1 (2%)
ATROPHY, NOS	3 (16%)	18 (38%)	24 (51%)
*EPIDIDYMIS	(20)	(50)	(49)
GRANULOMA, SPERMATIC		1 (2%)	
NECROSIS, FAT	1 (5%)	1 (2%)	

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

TABLE C1 (CONCLUDED)

	CONTROL (VEH) 01-M065	LOW DOSE 01-M066	HIGH DOSE 01-M067
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(20)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)
*PERICARDIUM	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)	2 (4%)	
*MESENTERY	(20)	(50)	(49)
PERIARTERITIS		2 (4%)	1 (2%)
ALL OTHER SYSTEMS			
DIAPHRAGM			
INFLAMMATION, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
AUTOLYSIS/NECROPSY PERF/NO HISTO			2
AUTOLYSIS/NO NECROPSY PERFORMED			1

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

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)
ABSCESS, NOS		1 (2%)	1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(19)	(48)	(50)
INFLAMMATION, NOS			1 (2%)
#LUNG	(20)	(50)	(50)
THROMBUS, ORGANIZED	1 (5%)		
PNEUMONIA, CHRONIC MURINE	14 (70%)	33 (66%)	37 (74%)
CALCIUM DEPOSIT	1 (5%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(50)	(50)
HEMATOPOIESIS	1 (5%)	2 (4%)	5 (10%)
#CERVICAL LYMPH NODE	(20)	(48)	(40)
INFLAMMATION, NOS			2 (5%)
ANGIECTASIS		2 (4%)	2 (5%)
#THYMUS	(18)	(43)	(36)
CYST, NOS			1 (3%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS			2 (4%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
#ENDOCARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
*AORTA	(20)	(50)	(50)
PERIARTERITIS		1 (2%)	
MEDIAL CALCIFICATION	1 (5%)	1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
PELIOSIS HEPATIS		3 (6%)	2 (4%)
METAMORPHOSIS FATTY	1 (5%)	4 (8%)	2 (4%)
FOCAL CELLULAR CHANGE		1 (2%)	
ANGIECTASIS	2 (10%)	5 (10%)	1 (2%)
*BILE DUCT	(20)	(50)	(50)
DILATATION, NOS		1 (2%)	2 (4%)
HYPERPLASIA, NOS	4 (20%)	7 (14%)	5 (10%)
#PANCREAS	(20)	(50)	(48)
PERIARTERITIS	1 (5%)	1 (2%)	2 (4%)
#STOMACH	(20)	(50)	(49)
ULCER, FOCAL			3 (6%)
CALCIUM DEPOSIT		2 (4%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, NOS	1 (5%)		1 (2%)
INFLAMMATION, CHRONIC	13 (65%)	7 (14%)	5 (10%)
NEPHROPATHY, TOXIC		27 (54%)	29 (58%)
CALCIUM DEPOSIT	1 (5%)	3 (6%)	1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(50)	(50)
ANGIECTASIS	3 (15%)	9 (18%)	3 (6%)
#ADRENAL CORTEX	(20)	(50)	(50)
DEGENERATION, NOS	4 (20%)	4 (8%)	2 (4%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
#THYROID	(19)	(48)	(48)
FOLLICULAR CYST, NOS	2 (11%)	2 (4%)	
HYPERPLASIA, C-CELL		1 (2%)	
#PARATHYROID	(18)	(49)	(48)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*VAGINA	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)	2 (4%)	
#UTERUS	(20)	(49)	(49)
HYDROMETRA	4 (20%)	5 (10%)	3 (6%)
INFLAMMATION, NOS	1 (5%)	1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(49)	(49)
HYPERPLASIA, CYSTIC	1 (5%)	1 (2%)	
#OVARY	(20)	(50)	(50)
CYST, NOS	1 (5%)	1 (2%)	1 (2%)
HEMORRHAGIC CYST		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(49)
HEMORRHAGE		6 (12%)	
ANGIECTASIS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERICARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)

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

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F065	LOW DOSE 01-F068	HIGH DOSE 01-F069
*MESENTERY	(20)	(50)	(50)
PERIARTERITIS	1 (5%)	1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		3	5

APPENDIX D

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

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH ENDOSULFAN

	CONTROL (VEH) 02-M072	LOW DOSE 02-M073	HIGH DOSE 02-M074
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
EPIDERMAL INCLUSION CYST	1 (5%)	1 (2%)	
INFLAMMATION, NOS		1 (2%)	2 (4%)
*SUBCUT TISSUE	(20)	(49)	(50)
ABSCESS, NOS		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
PNEUMONIA, CHRONIC MURINE	2 (10%)	3 (6%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(50)
AMYLOIDOSIS	4 (20%)	2 (4%)	3 (6%)
HEMATOPOIESIS	1 (5%)	2 (4%)	
#MESENTERIC L. NODE	(20)	(47)	(49)
INFLAMMATION, NOS		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(49)	(50)
THROMBUS, ORGANIZED			2 (4%)
PERIARTERITIS			1 (2%)
#MYOCARDIUM	(20)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M072	LOW DOSE 02-M073	HIGH DOSE 02-M074
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
AMYLOIDOSIS	1 (5%)		
HYPERPLASIA, NODULAR	1 (5%)		1 (2%)
ANGIECTASIS		1 (2%)	
#PANCREAS	(20)	(49)	(49)
CYST, NOS	1 (5%)		
ATROPHY, NOS	1 (5%)		
#COLON	(20)	(48)	(48)
NEMATODIASIS	1 (5%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
HYDRONEPHROSIS		12 (24%)	1 (2%)
CYST, NOS		3 (6%)	
PYELONEPHRITIS, NOS		2 (4%)	2 (4%)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC	12 (60%)	30 (61%)	27 (54%)
AMYLOIDOSIS	3 (15%)	3 (6%)	4 (8%)
CALCIUM DEPOSIT			1 (2%)
#URINARY BLADDER	(20)	(48)	(49)
CALCULUS, NOS			1 (2%)
INFLAMMATION, NOS			1 (2%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*PENIS	(20)	(49)	(50)
PHIMOSIS		1 (2%)	
*PREPUTIAL GLAND	(20)	(49)	(50)
INFLAMMATION, NOS		1 (2%)	
#PROSTATE	(20)	(45)	(49)
INFLAMMATION, NOS		1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 02-M072	LOW DOSE 02-M073	HIGH DOSE 02-M074
*TESTIS	(20)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
ATROPHY, NOS		2 (4%)	3 (6%)
*EPIDIDYMIS	(20)	(49)	(50)
GRANULOMA, SPERMATIC		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
AMYLOIDOSIS	6 (30%)	24 (49%)	24 (48%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	8	11
ANIMAL MISSING/NO NECROPSY PERF		1	
AUTO/NECROPSY PERF/HISTO PERF	2	3	5

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

	CONTROL (VEH) 02-F072	LOW DOSE 02-F075	HIGH DOSE 02-F076
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#CERVICAL LYMPH NODE	(20)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
#MESENTERIC L. NODE	(20)	(50)	(50)
ANGIECTASIS		2 (4%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)
INFLAMMATION, NOS		1 (2%)	
CALCIUM DEPOSIT			1 (2%)
HYPERPLASIA, NODULAR	2 (10%)		
ANGIECTASIS			2 (4%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#PANCREAS	(19)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS		1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F072	LOW DOSE 02-F075	HIGH DOSE 02-F076
#PANCREATIC DUCT	(19)	(50)	(50)
DILATATION, NOS			1 (2%)
#STOMACH	(20)	(50)	(50)
HYPERKERATOSIS	1 (5%)		1 (2%)
ACANTHOSIS	1 (5%)		1 (2%)
#ILEUM	(20)	(50)	(50)
HYPERPLASIA, NOS			2 (4%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
HYDRONEPHROSIS		2 (4%)	4 (8%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(50)	(50)
HYDROMETRA		9 (18%)	7 (14%)
INFLAMMATION, NOS	3 (15%)	13 (26%)	13 (26%)
#UTERUS/ENDOMETRIUM	(20)	(50)	(50)
HYPERPLASIA, CYSTIC	8 (40%)	15 (30%)	20 (40%)
#OVARY	(20)	(49)	(50)
CYST, NOS	3 (15%)	11 (22%)	17 (34%)
INFLAMMATION, NOS	3 (15%)	12 (24%)	12 (24%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(20)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	1 (2%)

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

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 02-F072	LOW DOSE 02-F075	HIGH DOSE 02-F076
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	5	3
AUTO/NECROPSY PERF/HISTO PERF			1

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

January 18, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and 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 organic chemistry, biostatistics, biochemistry, 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 NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which Endosulfan was reviewed.

After briefly describing the conditions of test, the primary reviewer noted the high mortality in both the treated male rats and mice, as well as among the control male mice. However, the female rats and mice survived sufficiently long to conclude that no carcinogenic effect was produced by Endosulfan. The secondary reviewer concurred with this critique.

A question was raised as to whether Endosulfan should be considered for retest because of the high mortality among the male animals. There was some uncertainty as to the present extent of use of Endosulfan. After additional discussion, the Subgroup recommended that Endosulfan be considered by the Chemical Selection Working Group to determine whether, under present selection criteria, it warrants further study.

It was moved that the report be accepted as written. The motion was seconded and approved unanimously.

Members Present Were:

Arnold Brown (Acting Chairman), Mayo Clinic
Lawrence Garfinkel, American Cancer Society
Joseph Highland, Environmental Defense Fund
Charles Kensler, Arthur D. Little Company
Verald K. Rowe, Dow Chemical, U.S.A.
Sheldon Samuels, Industrial Union Department, AFL-CIO
Louise Strong, University of Texas Health Sciences Center
Sidney Wolfe, Health Research Group

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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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