BB-486
TR-7155

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

007155

4/25/1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of the Mouse Oncogenicity Study on Endosulfan

TO: George LaPocca, PM-15
Registration Division, H7505C

FROM: Marcia van Gemert, Ph.D. 4/25/89
Acting Chief, HFAS Branch, H7509C

THRU: William Burnam
Acting Director, HED, H7509C

4/28/89

Chemical: Endosulfan

Caswell No: 420

Project No: 8-1094

Registration Division had requested that HFAS review the mouse oncogenicity and rangefinding studies on the compound Endosulfan.

Conclusions:

Under the conditions of the study, endosulfan was not oncogenic when fed to male and female Hoe:NMRMf mice for 24 months at levels of 2, 6, or 18 ppm. There were no overt signs of toxicity or dose-related effects on clinical observations, food consumption, hematology, clinical chemistry, urinalysis, organ weights, macroscopic pathology, or microscopic pathology. Decreased survival in high-dose females and body weight reduction in high-dose males throughout the study were considered to be compound-related effects. Histologically, the incidence of lymphosarcoma was high in dosed and control males and females. Based on the effects of Endosulfan on mortality at 18 ppm, the LOEL is 18 ppm and the NOEL is 6 ppm.

The classification of this study is Core Minimum.

007155

EPA: 66D80086
DYNAMAC No. 134-B
March 22, 1989

DATA EVALUATION RECORD

ENDOSULFAN

Chronic Toxicity/Oncogenicity
Feeding Study in Mice

APPROVED BY:

Robert J. Weir, Ph.D.
Acting Department Manager
Dynamac Corporation

Signature: [signature]

Date: 3/22/89

007155

EPA: 68D80056
DYNAMAC No. 134-E
March 22, 1989

DATA EVALUATION RECORD

ENDOSULFAN

Chronic Toxicity/Oncogenicity
Feeding Study in Mice

REVIEWED BY:

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Date: 3/27/89

DATA EVALUATION RECORD

GUIDELINE § 83-5

STUDY TYPE: Chronic toxicity/oncogenicity feeding study in mice.

ACCESSION/MRID NUMBER: 407924-01.

TEST MATERIAL: Endosulfan technical.

SYNONYM(S): Thiodan; Benzolpen; 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide.

STUDY NUMBER(S): 745; TOXN No. 83.01113; Hoechst Report No. A38008.

SPONSOR: Hoechst Celanese Corporation, North Somerville, NJ.

TESTING FACILITY: Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Frankfurt, Federal Republic of Germany.

TITLE OF REPORT: Endosulfan-Substance Technical (Code: HOE 002671 OI ZD97 0003) Carcinogenicity Study in Mice, 24 Month Feeding Study.

AUTHOR(S): Donaubauer, H.H.

REPORT ISSUED: April 6, 1988.

CONCLUSIONS: Under the conditions of the study, endosulfan was not oncogenic when fed to male and female Hoe:NMRKf mice for 24 months at levels of 2, 6, or 18 ppm. There were no overt signs of toxicity or dose-related effects on clinical observations, food consumption, hematology, clinical chemistry, urinalysis, organ weights, macroscopic pathology, or microscopic pathology. Decreased survival in high-dose females and body weight reduction in high-dose males throughout the study were considered to be compound-related effects. Histologically, the incidence of lymphosarcoma was high in dosed and control males and females. Based on the effects of endosulfan on mortality at 18 ppm, the LOEL is 18 ppm and the NOEL is 6 ppm.

Classification: Core minimum.

A. MATERIALS:

1. Test Compound: Endosulfan technical; description: solid brown flakes; code No.:Hoe 002671 OI ZD97 0003; purity: 97.9%.

2. Test Animals: Species: mice; strain: Hoe:NMRKf (SPF71); age: approximately 4 weeks; weight: males--23 g, females--22.5g at study initiation; source: Hoechst Breeding Colony, Frankfurt, West Germany.

B. STUDY DESIGN:

1. Animal Assignment: Following 7 days of acclimation, animals were assigned to the following test groups with a computerized randomization procedure:

Test Group	Dose in Diet (ppm)	Main Study (24 months) Males	Main Study (24 months) Females	Interim Sacrifices (12 & 18 months) Males	Interim Sacrifices (12 & 18 months) Females
1 Control	0	60	60	20	20
2 Low (LDT)	2	60	60	20	20
3 Mid (MDT)	6	60	60	20	20
4 High (HDT)	18	60	60	20	20

Mice were individually housed in an environmentally controlled room with a 12-hour light/dark cycle.

The dose levels selected for this study were based on a 3-month subchronic oral toxicity study (Huntingdon Research Center U.K., Report HST 229/831052) and a supplementary 42-day feeding study (HOECHST AG, study No. 744, Report No. 85.0024) in mice. In the subchronic study, mice were fed the test material at doses of 2, 6, 18, or 54 ppm in the diet. Mice receiving 54 ppm, equivalent to a mean daily intake of 7.4 mg/kg body weight, exhibited convulsions and salivation and 12/20 males and 10/20 females died within 6 weeks of study initiation. No mortality or other toxic effects were exhibited at the lower levels. The reported NOEL was 18 ppm, equivalent to a mean daily intake of 2.2 mg/kg body weight.

The supplementary 42-day feeding study, in which mice were fed the test material at doses of 18 ppm in the diet, was used to test the sensitivity of the mouse strain. Two of 10 female mice died on days 28 and 38; no other effects were reported. The maximum tolerated dose was considered to be 18 ppm (equivalent to a mean daily intake of 4.6 mg/kg body weight).

2. Diet Preparation: Premixes were prepared by dissolving appropriate amounts of the test compound in 20 g of vehicle (sesame oil DAB 7) and were then mixed with the appropriate amount of test diet at 14-day intervals. A premix with the same amount of sesame oil was prepared for the control animals. One kilogram of the endosulfan/sesame oil premix was added to additional feed weekly at the appropriate test diet concentrations. Storage conditions were not reported. During the study period, samples of the test compound were reanalyzed for content of active ingredient and samples of the treated food were collected and analyzed for stability, concentration, and homogeneity.

Results: Samples of the test compound analyzed four times during the study indicated that endosulfan was stable during the study duration (24 months) with content of active ingredient ranging from 96.7 to 97.9%. The mean recovery values of the compound from the test diet were 90.0, 91.7, and 93.3% of the nominal values for the 2-, 6- and 18-ppm diets, respectively (Table 1). Concentration analyses for the control diet mixtures were not provided. The test diet was found to be stable up to 14 days of storage (Table 2).

TABLE 1. Analysis of Concentration of Endosulfan in Test Diet[a]

Month	Mean Concentration (mg/kg) at			
	0 ppm	2 ppm	6 ppm	18 ppm
1	--[b]	2.0 ± 0.1	6.0 ± 0.2	17.1 ± 0.9
6	--	2.1 ± 0.1	5.8 ± 0.7	18.1 ± 1.9
12	--	1.7 ± 0.1	5.4 ± 0.3	16.2 ± 2.1
18	--	1.6 ± 0.1	4.8 ± 0.4	17.3 ± 0.5
24	--	1.8 ± 0.1	5.5 ± 0.1	15.5 ± 1.0
Overall	--	1.8 ± 0.2	5.5 ± 0.5	16.8 ± 1.0
% Recovery	--	90	91.7	93.3

[a]Individual mean concentrations, overall mean diet concentration, and percent recovery were calculated by the reviewers.

[b]No data for control (0 ppm) diet were provided.

TABLE 2. Analysis of Stability of Endosulfan Test Diet[a]

Month	Mean Concentration (mg/kg) at: 2 ppm on Day 0	2 ppm on Day 7	2 ppm on Day 14	6 ppm on Day 0	6 ppm on Day 7	6 ppm on Day 14	18 ppm on Day 0	18 ppm on Day 7	18 ppm on Day 14
Initial	1.93	1.89	2.05	6.13	6.18	6.71	18.2	17.6	18.5
3	1.82	2.42	1.88	5.64	6.33	6.44	17.3	17.7	16.2
6	1.69	1.66	1.84	5.41	6.27	6.75	16.1	15.3	15.4
12	1.89	1.82	1.92	4.92	6.32	6.04	18.4	15.2	16.2
18	1.71	1.59	1.81	4.70	4.71	5.86	17.0	15.2	17.1
24	1.81	1.64	1.69	5.49	4.81	5.14	14.3	15.3	15.3
Overall	1.8±0.1	1.8±0.3	1.9±0.1	5.4±0.5	5.8±0.8	6.2±0.6	16.9±1.5	16.1±1.2	16.5±1.2
% Recovery	90	90	95	90	97	103	94	89	92

[a]Individual mean concentrations, overall mean diet concentration and percent recovery were calculated by the reviewers.

3. Food and Water Consumption: Animals received food (Altromin-1321, standard pulverized diet) and water ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data. Body weights, hematology, clinical chemistry, and relative organ weights were analyzed using the parametric methods of Dunnett and Sidak and the nonparametric methods of Nimenyi/Dunnett and Nimenyi/Sidak. Reticulocyte counts were analyzed using the T-test and the Wilcoxon test. Kaplan Meier estimates and the Log-rank test were used for survival analyses.

5. Quality Assurance: A quality assurance statement was signed and dated April 22, 1988.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of morbidity and mortality. Mice were examined weekly for neurological disturbances, opacity of the refracting medium of the eyes, impairment of dental growth, and changes in the oral mucosa. All mice were individually examined for palpable masses monthly for 6 months and twice monthly thereafter until study termination.

Results: The cumulative mortality and percent survival data are summarized in Table 3. At study termination (106 weeks), survival among high-dose females (28%) was significantly ($p<0.05$) lower than survival among the control females (45%). Survival in other dosed females and all dosed males were comparable to controls ranging from 37 to 55%. Survival in dosed animals of the satellite groups sacrificed at 12 months was comparable to controls; no deaths were reported in dosed or control animals scheduled for interim sacrifice at 18 months.

It was reported that there were no abnormal clinical signs suggestive of a compound-related effect; individual data were not presented. It was reported that no neurological disturbances, impairments of dental growth, or changes in the oral mucosa were found in dosed animals.

Palpation of the skin was reported by the study author to reveal an equal number of masses in dosed and control mice; individual data were not reported.

TABLE 3. Cumulative Mortality and Percent Survival in Mice Fed Endosulfan for 24 Months[a]

Dose Group (ppm)	Mortality (Percent Survival) at Week				
	26	52	78	92	106
Males					
0	3 (95)	5 (92)	12 (80)	16 (73)	27 (55)
2	1 (98)	8 (87)	14 (77)	22 (63)	33 (45)
6	1 (98)	10 (83)	16 (73)	25 (58)	37 (38)
18	2 (97)	15 (75)	17 (72)	23 (62)	35 (42)
Females					
0	3 (95)	4 (93)	11 (82)	20 (67)	33 (45)
2	2 (97)	2 (97)	10 (83)	21 (65)	36 (40)
6	0 (100)	8 (87)	16 (73)	27 (55)	38 (37)
18	1 (98)	12 (80)	23 (62)	30 (50)	43 (28)*

[a]Percent survival was based on 60 mice/sex/dose of the main group.

*Significantly different from control values at $p < 0.05$.

2. Body Weight: Mice were weighed weekly.

Results: Table 4 presents mean body weight data at selected intervals. Body weights of males receiving 18 ppm were slightly but significantly ($p<0.05$) decreased from study weeks 2 to 17 and 26 to 31 when compared to concurrent controls; body weights of these animals remained slightly but nonsignificantly decreased thereafter to study termination. The body weights of other dosed males and all dosed females were similar to controls throughout the study.

3. Food Consumption and Compound Intake: Consumption was determined and mean daily diet consumption was calculated at the same intervals as body weight. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results: Food and mean compound consumption data at selected intervals are summarized in Table 5. Food consumption of dosed males and females were found to be similar to concurrent controls. Mean test compound intake was reported to be 0.28, 0.84, or 2.51 mg/kg/day for males receiving 2-, 6-, or 18-ppm endosulfan, respectively, and 0.32, 0.97 or 2.86 mg/kg/day for females receiving 2-, 6-, or 18-ppm endosulfan, respectively.

4. Ophthalmological Examinations: Ophthalmoscopic examinations were not performed but the opacity of the refracting medium of the eyes was observed weekly.

Results: These findings were similar in dosed and control mice.

5. Hematology and Clinical Chemistry: Blood was collected from the retro-orbital venus plexus of nonfasted mice at 6, 12, 18, and 24 months for hematology and at 12, 18, and 24 months for clinical analysis from 10 mice/sex/group. The CHECKED (X) parameters were examined:

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count[a]
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*		Coagulation:thromboplastin time (PT)
X	Reticulocyte count (RETIC)[a]		
	Red cell morphology		

*Recommended by Subdivision F (October 1982) Guidelines.
[a]Reticulocyte counts and differential leukocyte counts were determined from control and high-dose mice only.

TABLE 4. Representative Results of Mean Body Weights of Mice Fed Endosulfan for 24 Months[a]

Dose Group (ppm)	Mean Body Weight (g ± S.D.) at Week						
	1	13	26	52	78	92	104
				Males			
0	27 ± 2	35 ± 3	37 ± 3	38 ± 4	39 ± 3	38 ± 3	37 ± 3
2	26 ± 2	35 ± 3	37 ± 3	38 ± 4	38 ± 3	38 ± 3	37 ± 3
6	27 ± 2	35 ± 3	37 ± 4	39 ± 4	38 ± 3	37 ± 3	36 ± 3
18	25 ± 2	34 ± 3*	35 ± 4*	37 ± 3	37 ± 4	36 ± 4	35 ± 4
				Females			
0	23 ± 1	28 ± 2	30 ± 2	32 ± 2	34 ± 4	34 ± 3	34 ± 3
2	23 ± 1	28 ± 2	30 ± 2	32 ± 2	33 ± 3	33 ± 3	33 ± 3
6	23 ± 1	29 ± 2	30 ± 2	32 ± 3	34 ± 3	34 ± 3	34 ± 4
18	23 ± 1	29 ± 2	31 ± 2	32 ± 4	34 ± 2	33 ± 4	34 ± 4

[a]Based on mice of the main group.

*Significantly different from control values at $p < 0.05$.

TABLE 5. Representative Food and Compound Consumption of Mice Fed Endosulfan for 24 Months[a]

Dose Group (ppm)	Mean Food Consumption (g/day ± S.D.) at Week							Mean Compound Consumption (mg/kg/day)
	1	13	26	52	78	92	104	
				Males				
0	5.5 ± 0.5	5.1 ± 0.4	4.8 ± 0.4	4.8 ± 0.6	5.3 ± 0.4	5.4 ± 0.4	5.4 ± 1.0	0
2	5.5 ± 0.6	5.0 ± 0.5	4.7 ± 0.5	4.8 ± 0.4	5.3 ± 0.4	5.4 ± 0.4	5.5 ± 0.6	0.28
6	5.6 ± 0.5	5.0 ± 0.5	4.7 ± 0.9	5.0 ± 0.5	5.3 ± 0.5	5.5 ± 0.6	5.6 ± 0.5	0.84
18	5.4 ± 0.5	4.9 ± 0.4	4.4 ± 1.0	4.8 ± 0.5	4.9 ± 0.5	5.2 ± 0.4	5.2 ± 1.2	2.51
				Females				
0	5.4 ± 0.8	5.0 ± 0.8	4.9 ± 0.6	4.8 ± 0.7	5.5 ± 0.7	5.8 ± 0.8	5.9 ± 0.8	0
2	5.3 ± 0.6	4.7 ± 0.6	4.5 ± 0.5	4.5 ± 0.5	5.4 ± 0.5	5.4 ± 0.6	5.3 ± 1.1	0.32
6	5.3 ± 0.7	4.7 ± 0.6	4.7 ± 0.6	4.6 ± 0.6	5.4 ± 0.6	5.4 ± 0.6	5.7 ± 0.6	0.97
18	5.3 ± 0.6	4.9 ± 0.7	4.6 ± 0.8	4.8 ± 0.7	5.2 ± 0.6	5.5 ± 0.5	5.4 ± 0.8	2.86

[a]Based on mice of the main group.

Results: There were no effects of dosing on hematology parameters. The study author reported that hematological changes due to aging of the mice (leukemia) were found in dosed and control animals.

b. Clinical Chemistry:

	Electrolytes	Other
	Calcium*	Albumin*
	Chloride*	Albumin/globulin ratio
	Magnesium*	Blood creatinine*
	Phosphorus*	Blood urea nitrogen*
	Potassium*	Cholesterol*
	Sodium*	Globulins
		Glucose*
	Enzymes	Total bilirubin*
X	Alkaline phosphatase (ALP)	Direct bilirubin
	Cholinesterase	Total protein*
	Creatinine phosphokinase*	Triglycerides
	Lactic acid dehydrogenase	
X	Serum alanine aminotransferase (SGPT)*	
X	Serum aspartate aminotransferase (SGOT)*	
	Gamma glutamyltransferase (GGT)	

Results: There were no effects of dosing on the enzyme parameters measured.

6. Urinalysis: Urinalyses were not performed.

7. Tissue Residue Determinations: Sections of liver and kidney tissues from 10 mice/sex/group were collected at terminal sacrifice for residue determinations of α- and ß-endosulfan. Only organs without macroscopic findings were used.

Results: The tissue residue results were not reported.

8. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination of integument, orifices, eyes, and internal organs. The CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

*Recommended by Subdivision F (October 1982) Guidelines.

	Digestive System		Cardiovasc./Hemat.		Neurologic
	Tongue	X	Aorta*	XX	Brain
X	Salivary glands*	XX	Heart*	X	Peripheral nerve (sciatic nerve)*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (2 levels)
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen	X	Eyes (optic nerve)*
X	Jejunum*	X	Thymus		
X	Ileum*				
X	Cecum*				
X	Colon*				
X	Rectum		Urocenital		Glandular
XX	Liver*	XX	Kidneys*	XX	Adrenals*
X	Gallbladder*	X	Urinary bladder*		Lacrimal gland
X	Pancreas*	XX	Testes*	X	Mammary gland*
		X	Epididymides	X	Thyroids*
		X	Prostate		Parathyroids*
		X	Seminal vesicle		Harderian glands
	Respiratory	XX	Ovaries		
X	Trachea*	X	Uterus		
XX	Lung*				

	Other
	Bone (sternum)*
X	Skeletal muscle*
X	Skin
X	All gross lesions and masses
X	Nasal septum

Results:

a. Organ Weights: Absolute organ weights were not statistically analyzed by the study author. The relative lung and ovary weights of high-dose females were reported to be slightly but significantly ($p<0.05$) decreased at 12 months; the relative liver weights of high-dose males and relative ovary weights of high-dose females were found to be slightly but significantly ($p<0.05$) decreased at 18 months. These decreases were reported to be within the range of values for strain-matched historical controls and therefore were considered to be incidental changes. At 24 months, organ weights were similar in dosed and control males and females. Earlier changes in organ weights were not consistent over time or between sexes.

*Recommended by Subdivision F (October 1982) Guidelines.

b. Gross Pathology: The study author considered the incidence of gross lesions to be similar in dosed and control males and females.

c. Microscopic Pathology:

1) Nonneoplastic: Table 6 summarizes nonneoplastic findings in mice sacrificed at 24 months. Nonneoplastic findings at 12 and 18 months were reported by the study author to be unrelated to endosulfan administration. The nonneoplastic findings of dosed mice at 24 months were considered to be similar to concurrent controls or were considered to be normal age- and strain-related changes. The incidence of epithelial thickening in the urinary bladder was increased in dosed males and females; however, in the absence of a progression to clear proliferative change, this was considered to be of no toxicological importance.

2) Neoplastic: Table 7 summarizes neoplastic findings in mice sacrificed at 24 months. Neoplastic findings at 12 and 18 months were considered spontaneous and of no toxicological importance. Lymphosarcoma was the most commonly observed type of neoplasm among male and female mice. The incidence of these findings were similar in dosed and control mice, were considered to be normal age- and strain-related changes, and were not considered to be compound related.

D. STUDY AUTHOR'S CONCLUSIONS:

Dietary administration of endosulfan to male and female HOE:NMRI mice for 24 months at concentrations of 2, 6, or 18 ppm produced no overt compound-related signs of carcinogenicity. Body weight reduction was exhibited in high-dose males and increased mortality was exhibited in high-dose females. Minor changes in organ weights (lung, liver, and ovary) were observed in some high-dose males and females at 12 and 18 months only. Based on these results, the NOEL for endosulfan is 6 ppm.

TABLE 6. Representative Nonneoplastic Findings in Mice Fed Endosulfan for 24 Months[a]

Organ/Finding	Dose Level (ppm) Males 0	Males 2	Males 6	Males 18	Females 0	Females 2	Females 6	Females 18
Lungs	(58)[b]	(59)	(55)	(57)	(59)	(58)	(57)	(59)
Congested	13	24	17	16	16	5	18	20
Kidneys	(58)	(59)	(55)	(57)	(59)	(58)	(57)	(59)
Cortical cysts(s)	2	13	8	2	0	0	1	0
Cortical foci of mononuclear cells	3	5	4	12	3	3	0	0
Urinary bladder	(58)	(59)	(55)	(57)	(59)	(58)	(57)	(59)
Minimal focal epithelial thickening	0	5	8	12	0	6	9	10
Adrenals	(58)	(59)	(55)	(57)	(59)	(58)	(57)	(59)
Severe subcapsular foci of fibroblast-like cells	0	0	2	4	8	10	8	8
Areas of fatty degeneration	0	0	1	2	6	5	8	11
Seminal Vesicles	(58)	(59)	(55)	(57)				
Distended	13	15	21	20				
Distended with peripheral fibrosis	4	0	0	13				
Uterus					(59)	(58)	(57)	(59)
Prominent fibrous tissue					0	1	1	3
Dilated gland(s)					3	6	1	7

[a]Based on mice of the main group.

[b]Number in parentheses equals number of tissues examined.

TABLE 7. Representative Neoplastic Findings in Mice Fed Endosulfan for 24 Months

Organ/Finding	Dose Level (ppm)							
	Males				Females			
	0	2	6	18	0	2	6	18
Heart	(58)[a]	(59)	(55)	(57)	(58)	(58)	(57)	(58)
Lymphosarcoma	4	7	10	9	3	6	10	5
Lungs	(58)	(59)	(55)	(57)	(59)	(58)	(57)	(59)
Lymphosarcoma	9	7	12	10	8	14	11	9
Aorta	(53)	(54)	(49)	(50)	(55)	(51)	(50)	(49)
Lymphosarcoma	7	5	7	5	7	12	11	8
Spleen	(58)	(58)	(54)	(57)	(59)	(57)	(57)	(58)
Lymphosarcoma	10	11	12	9	9	17	16	11
Kidneys	(58)	(59)	(55)	(57)	(59)	(58)	(57)	(59)
Lymphosarcoma	9	8	9	8	7	10	10	9
Pancreas	(56)	(55)	(53)	(56)	(58)	(57)	(53)	(56)
Lymphosarcoma	5	4	5	2	5	11	10	6
Lymph nodes	(56)	(56)	(54)	(56)	(59)	(54)	(55)	(58)
Lymphosarcoma	11	13	15	13	16	20	22	11
Urinary bladder	(56)	(58)	(54)	(52)	(58)	(51)	(53)	(54)
Lymphosarcoma	1	3	3	2	3	6	6	3
Uterus					(59)	(58)	(57)	(59)
Lymphosarcoma					3	5	9	5
Ovaries					(59)	(56)	(56)	(59)
Granulosa cell tumor					6	10	11	13
Esophagus	(55)	(58)	(54)	(57)	(57)	(51)	(52)	(58)
Lymphosarcoma	1	5	3	2	2	4	4	5
Nasal cavity	(54)	(56)	(50)	(53)	(56)	(56)	(53)	(55)
Lymphosarcoma	0	3	4	3	0	2	3	3
Multicentric tumors	(17)	(16)	(20)	(17)	(26)	(29)	(27)	(18)
Lymphosarcoma	12	13	18	16	22	25	25	15
Lymphosarcoma as cause of death	11	8	14	11	10	16	15	11

[a]Number in parentheses equals number of tissues examined; missing tissues were subtracted from total tissues examined.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The study design was adequate for an oncogenicity study but not for a combined chronic toxicity/oncogenicity study, which were the guidelines referred to by the study author. There were some deficiencies in the conduct of the study and in data reporting. The control diet was not analyzed for concentration of test compound. Means, standard deviations, and percent recovery of the diet concentration and stability analyses were calculated by the reviewers. Homogeneity data were not reported. No statistical analysis was performed on absolute organ weights.

EPA Pesticide Assessment Guidelines, 1982, for chronic toxicity/oncogenicity studies suggest 15 clinical biochemistry determinations that should be performed on animals for chronic studies. Since sufficient blood was not available, only SGOT, SGPT, and alkaline phosphatase clinical biochemistry parameters were measured in this study. Urinalyses and complete ophthalmological examinations, which were not performed in this study, were also suggested in EPA Pesticide Assessment Guidelines.

Several discrepancies were reported in the histopathological data at 12 (1 discrepancy), 18 (1 discrepancy), and 24 months (5 discrepancies) involving numbers of missing tissues, numbers of tumor-bearing mice, and numbers of tumors in various tissues.

No intercurrent or sporadic deaths were indicated for 18-month satellite animals (10 mice/dose/sex); our reviewers consider this finding to be unusual. Histologically, the incidence of missing tissues appeared to be high in animals sacrificed at 12, 18, and 24 months; however, missing tissues were primarily from nonmajor organs.

It appears that an MTD was not achieved; the NOEL of 6 ppm was based on the effects of endosulfan on mortality and body weight at the high dose. However, survival was decreased in females only and body weights were only slightly decreased (1 to 2g) in males; these changes in body weight, although statistically significant, were not considered to be biologically significant by the reviewers. Dose levels for the study were based on results of a 3-month subchronic oral toxicity study in which convulsions and death were exhibited at 54 ppm, the highest dose tested. No toxic effects were exhibited at the lower doses tested, 2, 6, or 18 ppm. The reviewers suggest that a high-dose level of 36 ppm, for example, may have produced a greater incidence of compound-related effects.