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ETHOPROP: ADDENDUM TO DYNAMAC'S REVIEW OF CHRONIC TOXICITY AND ONCOGENIC POTENTIAL IN RATS (study conducted by Gulf South Research Institute, Baton Rouge, LA, report date 1/20/83, Study No. 413-858-41). EPA Record No. 115153. Accession No's: 263802-263807

Introduction

This Toxicology Branch reviewer is in general agreement with Dynamac's conclusions, recommendations, and the reviewer's discussion and interpretation of results with regard to this study (see Dynamac report sections 7, 8, and 14 respectively for specifics). The purpose of this addendum is to reiterate what additional data/information Dynamac has requested the sponsor to provide before this study can be evaluated further, to add some comments and to to ask the sponsor to provide some data/infonmation in addition to that requested by Dynamac.

1. As indicated by Dynamac, "the...numbers of individual animal tissues examined histologically for each organ or tissue in each group are needed in order to evaluate the histopathology data and oncogenic potential of Ethoprop".

2. The concentration of Ethoprop in the test diets was reported by the study authors to be $\pm$ 10% (actual concentrations may have been closer to $\pm$ 20%) of specifications. However, only 4 months of analytical data to verify this were included in the study report. The sponsor should explain why these data are not available, or if they are, submit them. Homogeneity data for the test diets were not submitted and are requested.

3. What was the rationale for dose selections in this study? Why was the decision made to choose this type of protocol over the more standard one?

4. F_0 generation breeding and litter data were not submitted and are requested.

5. Summary Incidence tables for gross pathology and clinical findings were not submitted and are requested.

6. The sponsor should specify the statistical method used to determine which test groups were statistically significantly different from others in a comparison.

7. Increases, with respect to controls, in white blood cell counts at interim sacrifice were observed in treated animals. In males, the increase was not dose-dependent with the level in the high dose group being only about 8% higher than the control group. In females, when statistical outliers were omitted from the mean calculation, the WBC in the high dose group was about 40% greater than in the control group. The possibility of a treatment related effect at 1 year cannot be ruled out but, by study termination, white blood cell counts in treated groups of males and females were similar to those of the respective controls.

8. Hematology and clinical chemistry determinations were made at interim sacrifice and at study termination. Cholinesterase activities were measured only at study termination. Determinations at additional time points (as is indicated in the Guidelines) would have helped to provide a more complete picture of the time course of effects on these parameters. The lack of these measurements is a weakness in this study.

9. Compared to controls, statistically significant decreases in the thyroid/body weight and liver/body weight group means of high dose females and males respectively and a statistically significant increase in the brain/body weight of high dose males were reported. Since the deviations are of such a relatively small magnitude, the significance of these findings, if any, is unclear. However, the possibility of a residual developmental effect of the test material cannot be excluded.

10. Although not specifically mentioned in the Dynamac review, it appears that a Maximum Tolerated Dose (MTD) was attained in this study (i.e. the Highest Dose Tested (HDT) of 18.0/196 ppm. The primary reasons for this determination are as follows:

a. Decrements in body weight gain compared to controls of about 16% from week 0 to week 52 and of about 10% from week 0 to week 109 were noted in high dose groups of both sexes;

b. Dose-related inhibition compared to controls of serum and brain cholinesterase was observed at week 109. The percent decrease in high dose group male serum and brain cholinesterase activity was about 86% and 68% respectively and for females 93% and 65% respectively.

c. Some clinical observations such as emaciation and rough haircoat were noted in some high dose animals.

Although there was some increased mortality during the first year in high dose males compared to controls it was not considered to be excessive (i.e. 85% survival for high dose versus 98% for control group at week 48). At the end of the study, mortality rates in high dose groups of males and females were similar to controls.

Conclusions

1. The chronic feeding portion of this study is considered by Toxicology Branch to be Core Supplementary. It cannot be upgraded since no NOEL for cholinesterase inhibition was observed. At all doses of Ethoprop tested, cholinesterase inhibition of >20% was noted.

As indicated in the above paragraphs, additional data have been requested of the sponsor with regard to the chronic toxicity portion of the study. Data/information necessary to satisfactorily address this request should be submitted.

In addition, Tox Branch would like to examine summary incidence tables for clinical observations. The clinical observation data submitted thus far are for indiviual animals, are in code, and occupy two data volumes.

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2. The oncogenicity portion of this study is considered by Toxicology Branch to be Core Supplementary. More data has been requested to evaluate potential oncogenicity, so that at this point a NOEL for oncogenicity cannot be established. If concerns regarding potential oncogenicity are satisfactorily addressed, this portion of the study may be upgraded.

EPA: 68-01-6561
TASK: 88
February 25, 1985

Correction Sheets

DATA EVALUATION RECORD

ETHOPROP

Chronic Toxicity/Oncogenicity Study in Rats

STUDY IDENTIFICATION: Barnett, J., Jenkins, L., Parent, R., et al. Evaluation of the chronic toxicity and oncogenic potential of ethoprop in Fischer 344 rats. (Unpublished Report No. 413-858-41 prepared by Gulf South Research Institute, New Iberia, LA for Rhone-Poulenc, Inc., Monmouth Junction, NJ; dated January, 1983.) Accession No. ~~252338-252363.~~ 263802-263807

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APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: _____

Date: _____

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1. CHEMICAL: Ethoprop, MOCAP (O-Ethyl-S,S-Dipropylphosphorodithioate), an organophosphorous pesticide.

2. TEST MATERIAL: Ethoprop, a colorless liquid concentrate containing 95.3% active ingredient, Lot No. MCTR 159-77.

3. STUDY/ACTION TYPE: Chronic toxicity and oncogenicity study in rats.

4. STUDY IDENTIFICATION: Barnett, J., Jenkins, L., Parent, R., et al. Evaluation of the chronic toxicity and oncogenic potential of ethoprop in Fischer 344 rats. (Unpublished Report No. 413-858-41 prepared by Gulf South Research Institute, New Iberia, LA for Rhone-Poulenc, Inc., Monmouth Junction, NJ; dated January, 1983.) Accession No. 252358-252363.

5. REVIEWED BY:

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7. CONCLUSIONS:

A. Under the conditions of this chronic toxicity study with Fischer 344 rats, there was an increase in the number of C-cell adenomas of the thyroid in males receiving the high-dose (18 ppm for 12 weeks and 196 ppm for 97 weeks)) when compared to controls, and there was a dose-related increase in the number of endometrial polyps in females. However, the total number of individual tissues examined histologically per group was not presented. Consequently, the incidence of these lesions cannot be determined or analyzed statistically, and an evaluation of the oncogenic potential of ethoprop cannot be performed. We suggest that this study be considered as supplementary data for both oncogenic and chronic toxicity testing. Plasma and brain cholinesterase inhibition was noted for all dosed animals. Therefore, the LOEL for cholinesterase inhibition is the low dose (4.5 ppm for 12 weeks and 49 ppm for 97 weeks) and a NOEL cannot be established. There were no other effects noted for animals receiving the low dose.

8. RECOMMENDATIONS:

A. The total numbers of individual animal tissues examined histologically for each organ or tissue in each group are needed in order to evaluate the histopathology data and oncogenic potential of ethoprop. It is also suggested that the sponsor provide the rationale for the unusual protocol used for this study, namely, exposing the animals to ethoprop in utero and during lactation by administering the test diet to the F_0 parents.

9. BACKGROUND: Not applicable.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES: Not applicable.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: See Appendix A.

Ethoprop, a colorless liquid concentrate formulation containing 95.3% active ingredient, was the material tested. Route of administration was via dosed feed.

Male and female Fischer 344 rats (F_1 generation) were exposed in utero and during the lactation period by administering the test diet to the F_0 parents.

The F_0 rats received diets containing 0, 60.5, 131, or 262 ppm of ethoprop. Following weaning, groups of 60 male and 60 female rats were assigned to the same selected treatment groups, and fed

the F_0 diet containing 0, 4.5, 9.0, or 18 ppm of ethoprop for 12 weeks, then placed on diets containing 0, 49, 98, or 196 ppm of ethoprop thereafter.

Animals were observed twice daily for toxic signs. Body weights and food consumption were measured weekly. Urinalysis, hematology and blood chemistry were measured on 10 rats/sex/group at 52 weeks, and on all survivors at week 109. Organ weights were recorded for the 10 rats/sex/group sacrificed at week 52 and on all survivors at study termination. It was also reported that a complete gross examination and histopathologic evaluation on a complete set of tissues were performed on all animals in the study. Data were statistically analyzed.

B. Protocol: See Appendix B.

12. REPORTED RESULTS:

F_0 Breeding and Litter Data: No compound/dose-related effects were noted for any of the F_0 reproductive indices, except for a slight decrease in the average number of offspring in the high-dose group (8.8) as compared to control animals (9.9). Body weight data indicated a compound-related decrease in the mean body weights of male and female offspring in the high-dose groups at weaning (corresponding to week 0 of the chronic study, Table 1). Body weight data of litters prior to culling and weaning were not presented.

Diet Analyses: Weekly diet preparation sheets were present throughout the study and indicated that the doses were accurately reported. However, diet analysis data were present for only the first 4 months of the study. The dietary concentrations of ethoprop were within acceptable limits of theoretical values (±20%). Ethoprop was found to be stable in the diets for more than 29 days.

Clinical Observations and Mortality: Emaciation and rough haircoat were noted in animals receiving the high dose. Lacrimation, chromodacryorrhea, eye protrusion, and opacity were also noted, but the incidences were similar among ethoprop-treated and control animals.

Increased mortality was noted in males receiving the high dose during the first year of the study, when compared to control animals (Table 2). At terminal sacrifice, the survival rates for all dosed male and female groups were similar to their respective control group. Survival at termination ranged between 53.3 - 63.3 percent.

TABLE 1. Selected Mean Body Weights of Rats Fed Diets Containing Ethoprop for Two Years

Dietary Level (ppm)	Group Mean Body Weight (gm) at Week						
	0	12	26	52	78	104	109
Males							
Control	56.9	270.0	328.1	392.8	390.3	376.7	370.4
4.5/49	55.1	267.6	321.3	384.0	388.8	383.8	362.3
9.0/98	55.2	257.8**	306.2**	361.6**	372.7**	375.3	368.3
18.0/196	50.6**	247.4**	281.2**	334.1**	337.3**	337.5**	329.2**
Females							
Control	51.1	163.4	190.7	233.6	259.7	277.7	273.4
4.5/49	51.8	161.2	191.7	233.1	264.7	289.6	274.0
9.0/98	49.9	156.9**	182.1**	217.9**	245.8**	277.3	272.3
18.0/196	46.2**	150.4**	169.7**	196.6**	220.2**	244.5**	246.0**

**Significantly different from control value at $p < 0.01$.

TABLE 2. Percent Survival of Rats Fed Diets Containing Ethoprop for 109 Weeks

Dietary Level (ppm)	Percent Survival (No. of dead animals) at Week					
	12	48	52[a]	56	104	109
Males						
Control	98.3(1)	98.3(1)	81.7(1)	81.7(1)	68.3(9)	56.7(16)
4.5/49	98.3(1)	98.3(1)	81.7(1)	81.7(1)	65.0(11)	60.0(14)
9.0/98	98.3(1)	95.0(3)	78.3(3)	76.7(4)	60.0(14)	58.3(15)
18.0/196	90.0(6)	85.0(9)**	81.7(9)	68.3(9)	61.7(13)	60.0(14)
Females						
Control	100(0)	100(0)	100(0)	81.7(0)	61.0(13)[b]	57.6(15)[b]
4.5/49	96.7(2)	96.7(2)	96.7(2)	78.3(3)	70.0(3)	63.3(12)
9.0/98	95.0(3)	95.0(3)	95.0(3)	78.3(3)	60.0(14)	58.3(15)
18.0/196	93.3(4)	93.3(4)	93.3(4)	76.7(4)	61.7(13)	53.3(18)

[a] Interim sacrifice animals (10/sex/group) included in percent survival calculations at week 52.

[b] Value corrected by reviewers.

** Significantly different from control value at $p < 0.01$.

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Body Weight Determinations: The initial body weights of male and female rats in the high-dose group were significantly lower ($p < 0.01$) than those of their respective controls (Table 1). These rats had significantly lower body weights (and body weight gains) than control animals throughout the study. A significant decrease ($p < 0.05$) in the mean body weights of male and female rats receiving the mid dose was also noted by week 2. Lower mean body weights (and body weight gains) for mid-dose males and females were noted throughout weeks 94-97 of the study, after which the animals recovered. The mean body weights of animals receiving the low dose was similar to those of controls throughout the study.

Food and Water Consumption: A general trend towards reduced food consumption was noted in males and females receiving the high dose during the first year of the study (Table 3). Other significant differences were noted, but these did not follow a specific time- or dose-related trend. The mean consumption of test material throughout the study is presented in Table 4. Water consumption was determined during the latter part of the study (weeks 102-109). There were no differences noted in water consumption between control and ethoprop-dosed rats.

Hematology: Compound-related decreases in red blood cell counts, hematocrit, and hemoglobin were observed in males and females at interim sacrifice when compared to control values. However, the report stated that all values were within the normal range. In addition, increased leukocyte counts were observed in all dosed male and female animals at interim sacrifice. There were no compound-related changes in hematology values at final sacrifice.

Blood Chemistry: There were no compound-related changes in blood chemistry values of males or females at interim sacrifice. At final sacrifice, a significant decrease in glucose levels was noted in males receiving the low and high doses and a decrease in protein levels was noted in females receiving the high dose, when compared to controls.

Cholinesterase Activity: Cholinesterase activity was determined in animals at final sacrifice. There was a dose-related inhibition of serum and brain cholinesterase activities in treated animals when compared to controls (Table 5). Cholinesterase activity in erythrocytes was similar among control and dosed animals.

Urinalysis: There were no compound-related effects in urine chemistry values and microscopic examination of urine sediments of males and females at the interim or final sacrifices.

TABLE 3. Selected Mean Food Consumption of Rats Fed Diets Containing Ethoprop for 109 Weeks

Dietary Level (ppm)	Mean Food Consumption (gm/rat/week) at Week						
	1	12	26	52	78	104[a]	109
Males							
Control	40.4	76.9	89.4	58.5	90.1	87.0	92.4
4.5/49	41.4	74.3	90.4	55.2	88.1	92.5	92.6
9.0/98	42.1	77.6	85.0**	73.4**	76.0**	90.1	94.4
18.0/196	43.7*	71.1**	81.9**	74.2**	59.2**	86.1	93.7
Females							
Control	35.4	67.4	72.2	52.8	74.7	84.1	82.4
4.5/49	39.6**	64.8	71.3	46.3	78.1	83.5	79.9
9.0/98	36.1	58.3**	70.2	63.2*	51.1**	93.3**	88.5
18.0/196	38.6**	57.2**	69.8	62.8*	45.7**	86.2	86.7

* Significantly different from control value at $p < 0.05$.
** Significantly different from control value at $p < 0.01$.

TABLE 4. Selected Mean Test Material Consumption of Rats Fed Diets Containing Ethoprop for 109 Weeks

Dietary Level (ppm)	Mean Test Material Consumption (mg/kg) at Week					
	1	13	26	52	104	109
Males						
4.5/49	2.5	13.3	13.8	7.4	11.8	12.8
9.0/98	5.1	29.6	27.2	19.8	23.7	25.3
18.0/196	11.4	61.4	57.3	43.7	50.5	56.7
Females						
4.5/49	2.6	18.8	18.2	9.7	14.2	14.4
9.0/98	4.9	35.6	37.8	28.4	33.3	31.9
18.0/196	11.5	77.8	80.8	62.8	69.4	69.5

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TABLE 5. Cholinesterase Activity Determinations in Rats Fed Diets Containing Ethoprop for 109 Weeks

Dietary Level (ppm)	Cholinesterase Activity (U/l or U/g)		
	Serum	RBC	Brain
Males			
Control	1722±270	140.1± 75.2	0.22± 0.03
4.5/49	321±173** (81%)[a]	130.4± 62.4	0.14± 0.02 (36%)
9.0/98	277±105** (84%)	130.0± 60.0	0.12± 0.02** (45%)
18.0/196	243±200** (86%)	137.9± 66.0	0.07± 0.01** (68%)
Females			
Control	2902±774	123.0±68.6	0.20±0.02
4.5/49	326±254** (89%)	116.0 ±62.3	0.14±0.03** (30%)
9.0/98	262±50** (91%)	111.6 ±64.1	0.10±0.03** (50%)
18.0/196	205±219** (93%)	132.8±60.8	0.07±0.02** (65%)

**Significantly lower than control value at $p < 0.01$.
[a]Number in parenthesis is the ~~percent of control values.~~ percent decrease in activity relative to the control group. KLH

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Gross Examination: A few isolated lesions were noted in animals sacrificed at the one-year interim sacrifice. The most common finding was distension of the uterine horns with clear fluid in females receiving the low and high doses. At the final sacrifice, gross lesions were correlated with microscopic findings but summary data were not presented. Common gross findings were reported to include bilateral multiple masses of the testes in males, enlargement or congestion of the pituitary gland, pale tan discoloration of the liver and kidneys of both male and female animals, and a number of soft peduncular tissue masses on the uterine horns. These lesions were observed in control and dosed groups with no apparent group differences.

Organ Weights: A few changes in mean organ weights were noted in dosed animals when compared to controls at interim sacrifice. The following organ weight changes were noted in males: lower kidney and adrenal weights in animals receiving the low dose; lower adrenal and testes weights in animals receiving the mid dose; and lower heart and kidney weights for animals receiving the high dose. In females, lower heart and liver weights and slightly higher spleen and ovary weights were observed in animals receiving the high dose.

Organ-to-body weight ratios of interim sacrifice animals also indicated some differences among dosed and control animals. Slightly higher ratios were noted for the thyroid and spleen in males receiving the high dose, thyroid and ovaries of all dosed female groups, and spleen of females receiving the high dose.

At final sacrifice, lower mean brain and testes weights were noted in males receiving the high dose, and lower mean heart, liver, kidney and lung weights noted in males receiving the mid and high doses (Table 6). In females, lower mean thyroid, heart, and liver weights were noted in animals receiving the high dose and lower kidney weights noted in animals receiving the mid and high doses (Table 7).

Organ-to-body weight ratios of animals at final sacrifice also showed some differences among control and dosed animals (Tables 6,7). These included significant relative weight ratios of the following organs: the liver and brain in males receiving the high dose; heart and kidney in males receiving the mid dose; thyroid of females receiving the high dose; and kidneys of females receiving the mid dose (Table 7).

Histopathology: There were no significant differences in histopathologic lesions noted between control and compound-treated animals at interim sacrifice. Histopathologic findings for animals that died during the study, sacrificed moribund, or sacrificed at study termination could not be fully evaluated because the number of individual tissues examined in each dose group were not reported.

TABLE 6. Mean Organ Weight Data at Study Termination for Male Rats Fed Diets Containing Ethoprop for 109 Weeks

Dietary Level (ppm)	Organ Weight Data						
	Body	Heart	Liver	Kidneys	Brain	Lung	Testes
			Mean Organ Weights (g)				
Control	370.4	1.1	12.1	2.8	1.99	1.40	6.9
±S.D.	23.4	0.1	1.8	0.2	0.08	0.12	1.5
4.5/49	361.1	1.0	11.8	2.8	1.99	1.38	6.2
±S.D.	47.5	0.1	2.3	0.3	0.10	0.16	2.2
9.0/98	368.3	1.0*	11.1*	2.6**	1.99	1.33*	6.6
±S.D.	23.9	0.1	1.8	0.2	0.07	0.17	1.6
18.0/196	333.3**	0.9**	9.6**	2.4**	1.94*	1.25**	6.0*
±S.D.	32.6	0.1	1.6	0.2	0.07	0.13	1.7
			Mean Organ/Body Weight Ratios ($\times 10^{-3}$)				
Control		2.872	32.77	7.649	5.398	3.793	18.67
4.5/49		2.853	32.93	7.838	5.502	3.810	17.32
9.0/98		2.707*	30.14	7.197**	5.382	3.610	18.00
18.0/196		2.792	28.64**	7.254	5.830*	3.743	18.00

*Significantly different from control value at $p < 0.05$.
**Significantly different from control value at $p < 0.01$.
a ~~Some~~ values in this table were rounded
Real values are in ( ) parentheses KLH

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TABLE 7. Mean Organ Weight Data at Study Termination for Female Rats Fed Diets Containing Ethoprop for 109 Weeks

Dietary Level (ppm)	Body	Thyroid	Heart	Liver	Kidney
			Mean Organ Weights (g)		
Control	269.9	0.032	0.9	9.2	2.1
± S.D.	40.3	0.009	0.1	2.5	0.3
4.5/49	273.4	0.035	0.9	9.6	2.1
± S.D.	30.3	0.011	0.1	2.0	0.2
9.0/98	272.5	0.030	0.9	8.8	2.0*
± S.D.	29.8	0.008	0.1	1.5	0.2
18.0/196	247.2**	0.025**	0.8**	8.0*	1.9**
± S.D.	21.3	0.008	0.1	1.7	0.2
			Mean Organ/Body Weight Ratios ($\times 10^{-3}$)		
Control		0.119	3.377	34.59	8.171
4.5/49		0.127	3.292	35.64	7.946
9.0/98		0.112	3.168	32.54	7.467*
18.0/196		0.100*	3.290	32.38	7.709

*Significantly different from control value at $p < 0.05$.
**Significantly different from control value at $p < 0.01$.

Consequently, the incidence of a specific lesion could not be determined and statistical analyses could not be performed. In addition, individual animal data were not reported for 3, 5, 6, and 1 males and 6, 2, 10, and 4 females in the control, low-, mid-, and high-dose groups, respectively.

A summary of the most frequently observed nonneoplastic lesions in each group are listed in Table 8. There was an increased number of animals from the high-dose groups with scleral and peripheral lenticular mineralization. Neoplastic lesions are listed in Table 9. There was an increased number of C-cell adenomas of the thyroid in males from the high-dose group when compared to the control animals. In addition, a dose-related increase in the number of endometrial polyps was noted in females. The number of animals with other lesions were similar among control and compound-treated females.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that "the following findings were considered to be directly attributable to the administration of the test material to Fischer 344 rats. Administration at the lowest dose level of 49 ppm resulted in no toxicologic signs other than a reduction in brain and serum cholinesterase levels. Minimal toxicity was observed at the mid-dose of 98 ppm as evidenced by reductions in the body weights and serum and brain cholinesterase levels. The high-dose of 196 ppm was moderately toxic, causing significant depressions in mean body weights and cholinesterase levels in both sexes.

The gross and microscopic pathology findings did not reveal marked increases in any particular lesion which was attributable to test material administration in the treated groups compared to controls."

B. A quality assurance statement was present, signed, and dated January 20, 1983. It indicated that the final report was checked for accuracy and inclusion of information, adherence to protocol, presentation of data, interpretations, and conclusions.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. This chronic toxicity study was conducted in an unusual manner in that the animals were exposed to the test material *in utero* and during the lactation period by administrating the test diet to the F_0 parents prior to the two-year feeding study. Although such studies have been performed with other chemicals, they are not required by EPA in support of pesticide registration and historical data may not be available. If this type of study is used, the rationale and historical data should be presented in the report.

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TABLE 8. Summary of Most Frequently Observed Nonneoplastic Lesions in Rats Fed Diets Containing Ethoprop for 109 Weeks

Organ/Lesion	Number of Animals Affected Per Dose Level (ppm)							
	Males				Females			
	0	49	98	196	0	49	98	196
Liver								
Adenofibrosis	33	26	20	15	16	11	4	0
Multifocal granuloma	7	2	7	7	11	11	4	6
Basophilic foci	2	5	7	2	10	6	2	1
Lung								
Peribronchial lymphoid aggregates	18	9	1	18	14	9	3	4
Perivascular granulomas	13	11	3	8	16	10	2	6
Kidney								
Murine nephrosis	10	11	2	1	7	7	0	2
Heart								
Cardiomyopathy	2	3	0	2	3	0	0	2
Testes								
Atrophy	0	1	3	0	-	-	-	-
Spleen								
Hematopoiesis	0	0	0	0	2	0	0	1
Adrenal								
Cortical nodular hyperplasia	0	0	1	0	1	1	0	0
Uterus								
Cystic glandular hyperlasia	-	-	-	-	0	3	1	1
Mesenteric lymph node								
Lymphadenitis	6	2	0	4	1	0	0	0
Eye								
Scleral mineralization	0	0	0	5	0	0	0	0
Peripheral lenticular mineralization	1	1	1	3	4	0	0	1
Retinal degeneration	0	0	3	0	0	0	0	0

TABLE 9. Summary of Most Frequently Observed Neoplastic Lesions in Rats Fed Diets Containing Ethoprop for 109 Weeks

Organ/Lesion	Number of Animals Affected Per Dose Level (ppm)							
	Males				Females			
	0	49	98	196	0	49	98	196
Liver								
Neoplastic nodule	3	0	0	1	1	1	3	3
Lymphosarcoma	0	0	1	1	0	1	0	1
Leukemia	5	1	4	2	5	4	2	5
Lung								
Alveolar adenoma	2	2	0	0	0	1	0	1
Leukemia	4	1	2	2	5	4	1	5
Kidney								
Lymphosarcoma	0	0	0	1	0	1	0	0
Adenocarcinoma	0	1	0	0	0	0	0	0
Pituitary								
Adenoma	12	14	9	9	24	26	20	20
Thyroid								
C-cell adenoma	3	4	1	10	2	7	2	4
C-cell hyperplasia	1	1	0	1	0	3	3	4
Testes								
Interstitial cell adenoma	42	38	36	38	-	-	-	-
Pancreas								
Islet cell adenoma	1	1	1	0	0	0	0	1
Adrenal								
Adenoma	0	1	1	0	0	0	0	0
Mammary gland								
Fibroadenoma	0	1	0	0	2	0	0	0
Uterus								
Stromal polyp	-	-	-	-	8	1	2	3
Endometrial polyp	-	-	-	-	0	4	8	13
Endometrial adenoma	-	-	-	-	0	0	0	2
Endometrial adenocarcinoma	-	-	-	-	1	0	0	2

A major deficiency in this study is the absence of information on the number of individual tissues examined in each group. Thus, the incidence of a specific lesion cannot be determined and statistical analyses of the data cannot be performed. Nonetheless, histopathology data indicated an increased number of C-cell adenomas of the thyroid in males receiving the high dose when compared to the control, and a dose-related increase in the number of endometrial polyps in females.

The results of this study also indicated lower body weights for male animals receiving the mid and high doses and females receiving the high dose when compared to control. This effect (is) maybe associated with in utero exposure or exposure via mothers milk during lactation. Increased mortality was also noted during the first year of the study in males receiving the high dose. At interim sacrifice, hematology data indicated anemic signs in males receiving the mid dose and in animals of both sexes receiving the high dose. However, at final sacrifice all values were similar to those of controls. Blood chemistry and urinalysis values were similar among compound-treated and control animals at interim and terminal sacrifice. Plasma and brain cholinesterase inhibition was noted in all compound-treated animals at final sacrifice. Consequently, the LOEL for cholinesterase inhibition is the low dose (4.5 ppm for 12 weeks and 49 ppm for 97 weeks) and a NOEL cannot be established. Lower organ weights in dosed animals is probably associated with the lower body weights of dosed animals. However, significantly lower organ-to-body weight ratios were also noted for liver, kidneys, and brain. Thyroid (high dose ♀) (mid dose ♂) (high dose ♂) and a significantly higher ratio for brain was noted in high dose males. A number of other deficiencies were also noted; individual data for F_0 breeding and litters were not presented, diet analysis was only performed during the first 4 months of the study, summaries of clinical observations and gross findings for animals in the two-year study were not presented, cholinesterase activity was not determined during the study (e.g., 1 year) and clinical chemistry was not determined at months 6 and 18 of the study. KLH

15. COMPLETION OF ONE-LINER FORM FOR STUDY: Not applicable.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI Volume I, pp. 2-8.
Appendix B, Protocol, CBI Volume II, pp. 2-4.

APPENDIX A

Materials and Methods

• EPA Registration Number 7401-97

Page _____ is not included in this copy of the registration file for the product.

Pages 19 ~~22~~ through 25 ~~28~~ are not included in this copy of the registration file for the product.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

√ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commerical/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

___ FIFRA registration data (*)

The information not included generally is considered confidential by product registrants. If you wish to obtain the information deleted, please contact the individual who prepared this response to your request.

(*) FIFRA registration data can be released to individuals who submit an Affirmation of Non-Multinational Status.

19, 23, 24, 25, 26, 27, 28

Appendix B
Protocol

• EPA Registration Number 2116-87

Page _____ is not included in this copy of the registration file for the product.

Pages 28 through 29 are not included in this copy of the registration file for the product.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

✓ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commerical/financial information

___ A draft product label

___ The product confidential statement of formula

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