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DATA EVALUATION REPORT

STUDY TYPE: Mouse Oncogenicity Study

MRID NO.: 50290 TOX. CHEM. No.: 320

TESTING FACILITY: CDC Research, Inc.

CITATION: Field, W.E. (1979) Oncogenicity Study in Mice with 2,4-DP Acid: Study No. CDC-AM-002-77. Final Rept. Unpublished study received Mar 13, 1980 under 264-222; prepared by CDC Research, Inc., submitted by Union Carbide Agricultural Products Co., Inc., Ambler, Pa.; CDL:242035-A; 242036; 242037; 242038)

CONCLUSION: Groups of CD-1 mice (50/sex/dose and 90/sex for controls) were administered 2,4-DP acid in diet at doses of 0, 25, 100, and 300 mg/kg for 18 months. Hematology parameters, body weight, food consumption, and survival rates of treated mice were comparable to those of the controls. According to the reported data, at 300 mg/kg, significant increases in absolute and relative liver weights and in the incidence of non-neoplastic lesions in the liver and biliary system were observed in males. The LEL for the toxicity of 2,4-DP acid was 25 mg/kg (LDT); NOEL could not be established.

There was no increase in tumor incidence in any group of the treated mice relative to that of the controls.

This study has many deficiencies which include:

1) The purity and chemical analysis data of the test agent were not reported.
2) No explanation was given concerning how the values of the doses (i.e. mg/kg) were derived since no chemical analyses for stability and concentration of the test compound in the diet were carried out.
3) Statistical analyses were not conducted.
4) Discrepancies were found in mean body weight data and in individual animal data.
5) The highest dose used in the study did not reach maximum tolerated dose (MTD).
6) Inconsistent histopathological diagonsis was used.
7) Discrepancies in tabulated and individual animal histopathology data prevented verification of these data.

This study is, thus, classified as supplementary.

A. MATERIALS:

1. Test compound: According to the report that technical 2,4-DP acid was analyzed, but the results were not presented. The batch No. was stated as EPA EST No. 15440 EN-1. Purity and other descriptions of the compound were not reported.

2. Test animals: Swiss-Webster derived CD-1 mice were obtained from Charles River Breeding Laboratories, Inc.; these animals were approximately 6 weeks old and weighed 10-12 gm.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (mg/kg)*	Main Study 18 months male	female
1 Cont.	0	90	90
2 Low (LDT)	25	50	50
3 Mid (MDT)	100	50	50
4 High(HDT)	300	50	50

* The report did not indicate how these dosages were achieved (i.e. whether they were calculated from food consumption data or other parameters).

2. Diet preparation: According to the report, the compound was mixed with the feed, but the data on the stability and concentration of the compound in the diet were not reported.

3. Animals received food and water ad libitum.

4. Statistics: The report did not indicate any statistical procedures were ever used.

5. Quality assurance statement was not presented.

C. METHODS AND MATERIALS:

1. Observations

Animals were inspected daily at the beginning of the study, and subsequently they were examined twice daily for toxicity and mortality.

The survival rates of all the animals are presented in Table 1. Although the survival rates of mid and high dose males are slightly lower than that of the controls, there were no dose related trends and statistical significance.

Increases in compound-related toxic signs were not observed in the treated animals relative to the controls.

TABLE 1*

Survival Rates of 2,4-DP Acid Treated and Control Mice

Dose (mg/kg)	0	20	100	300
Males	79/90 (88)	42/50 (84)	36/50 (72)	39/50 (78)
Females	68/90 (76)	41/50 (82)	35/50 (70)	36/50 (72)

( ): percentage

*: Data abstrated from submission (MRID No. 50290)

2. Body Weight

Animals were weighed weekly for 13 weeks pretest and monthly for the rest of the test period. The body weight data of the treated and control animals are presented in Table 2.

No body weight changes were observed in either treated males or females relative to the controls.

It should be noted that there are discrepancies in the values of mean body weights as presented in Tables 2 and 5 (Tables 4 and 7 in the submission). The final mean body weights presented along with the mean organ weights (Table 5) should be similar to those presented in Table 2. In Addition, the values presented in Table 2 could not be validated with the individual animal data.

TABLE 2*

Mean Body Weight

Males

Group 1

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	23	27	29	31	32	33	33	35	35	36	36	37	37	38	38	39	40

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	41	40	41	41	40	42	42	43	44	42	43	43	44	42

Group 2

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	23	27	29	31	33	34	35	35	36	36	36	37	37	38	38	39	40

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	42	41	42	42	42	42	42	44	44	43	43	43	43	41

Group 3

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	22	26	28	30	32	33	34	35	36	37	37	37	37	38	38	40	42

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	43	42	42	43	43	43	43	44	45	44	44	44	44	44

Group 4

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	22	26	29	30	32	33	33	34	35	36	36	37	37	37	38	39	40

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	42	41	42	42	43	43	43	44	44	43	43	44	43	43

*DATA TAKEN From the Submission (MRID No. 50290)

TABLE 2 (cont'd)*

Mean Body Weight

Females

Group 1

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	20	23	24	25	26	27	27	28	28	29	29	30	30	31	31	32	33

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	34	34	35	35	35	36	36	37	38	37	38	38	38	37

Group 2

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	21	23	24	25	26	27	28	28	29	29	29	30	29	30	31	32	33

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	34	33	34	35	35	36	35	37	37	37	38	37	38	38

Group 3

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	20	22	23	24	25	26	26	27	27	28	29	29	29	29	30	32	33

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	35	34	35	35	36	36	36	37	38	37	38	38	39	38

Group 4

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25
Grams:	18	22	23	24	25	27	27	28	28	29	29	29	29	29	30	32	32

Weeks:	29	33	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	33	33	33	33	34	34	35	33	36	36	36	35	36	37

*DATA TAKEN From the Submission (MRID No. 50290)

TABLE 3*

Mean Food Consumption

Males

Group 1

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	10	11	11	11	10	7	7	8	7	7	8	6	7	7	7	6	6	7	6

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	6	6	6	6	5	5	5	6	6	5	6	5

Group 2

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	10	9	10	9	10	7	9	6	7	7	7	7	7	7	6	5	5	5	6

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	6	6	5	5	5	5	5	5	6	5	5	5

Group 3

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	7	7	7	7	9	6	8	5	6	6	6	6	6	6	6	5	4	5	6

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	5	6	5	5	5	5	5	5	5	4	5	5

Group 4

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	11	9	9	7	10	7	8	6	7	7	7	6	7	6	6	5	5	5	5

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	5	5	6	5	5	5	4	5	5	5	5	5

* : DATA TAKEN FROM THE Submission (MRID NO. 50290)

TABLE 3 (Cont'd)*

Mean Food Consumption

Cont.

Females

Group 1

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	10	13	13	12	11	8	9	8	9	10	10	9	9	9	9	7	8	8	8

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	7	8	7	6	6	6	6	6	6	5	6	5

Group 2

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	10	7	11	10	10	8	8	6	7	8	7	7	7	8	7	6	5	5	6

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	6	5	5	5	5	5	5	5	5	5	5	5

Group 3

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams	15	10	11	9	9	8	9	8	9	8	9	8	9	8	8	8	6	7	7

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	6	5	5	5	5	5	5	5	5	5	5	5

Group 4

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	17	21	25	29	33
Grams:	10	12	14	12	12	8	10	7	10	9	11	8	9	9	8	7	6	7	6

Weeks:	37	41	45	49	53	57	61	65	69	73	77	81
Grams:	6	6	6	5	5	5	4	5	6	5	5	5

*: DATA TAKEN FROM THE SUBMISSION (MRID No. 50290)

3. Food Consumption:

Food consumption was calculated and presented as mean weekly food consumption (Table 3). There was essentially no difference in the amount of food consumed by the treated mice relative to the controls.

4. Ophthalmological Examinations: No results were reported.

5. Blood was collected at the termination of the study for hematology from 10 mice/sex/dose. The CHECKED (X) parameters were examined.

a. Hematology

|x|	Hematocrit (HCT)*	|x|	Leukocyte differential count*
|x|	Hemoglobin (HGB)*	| |	Mean corpuscular HGB (MCH)
|x|	Leukocyte count (WBC)*	| |	Mean corpuscular HGB conc.(MCHC)
|x|	Erythrocyte count (RBC)*	|x|	Mean corpuscular volume (MCV)
|x|	Platelet count*	| |	Reticulocyte count
| |	Blood Clotting Measurements		
| |	(Thromboplastin time)		
| |	(Clotting time)		
| |	(Prothrombin time)		

* Required for subchronic and chronic studies

The results of hematological studies are presented in Table 4. No changes in the hematological parameters were found in treated animals relative to the controls.

b. Clinical Chemistry: No clinical chemistry was conducted. Clinical chemistry study is generally not required for a mouse oncogenicity study because of the limited volume of the blood available from a mouse.

c. Urinalysis: This analysis was not conducted. For a mouse oncogenicity study, urinalysis is generally not required.

TABLE 4*

Summary of Hematologic Evaluations

MALES

Dose Group	N		HCT	HGB	RBC	WBC	MCV
1	10		32.90	11.90	6.01	4.40	54.00
		S.D.	6.65	1.50	1.13	1.71	2.88
2	10		32.70	12.00	6.05	5.20	54.00
		S.D.	3.05	1.00	0.62	1.85	1.94
3	10		32.10	12.20	6.03	5.00	53.00
		S.D.	3.82	0.62	0.63	2.18	1.10
4	10		34.00	12.10	6.27	5.00	54.00
		S.D.	2.63	0.68	0.38	2.05	1.15

FEMALES

1	10		31.90	11.80	5.83	3.60	54.00
		S.D.	4.25	1.13	0.68	1.79	1.72
2	10		36.10	12.90	6.51	3.50	55.00
		S.D.	5.46	1.98	0.77	1.79	2.23
3	10		32.50	12.10	5.98	5.50	54.00
		S.D.	1.91	0.67	0.30	2.24	1.63
4	10		31.20	11.40	5.74	5.10	54.00
		S.D.	2.94	0.90	0.53	3.30	1.93

*DATA TAKEN From the submission! (MRID No. 50290)

7. Sacrifice and Pathology:

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

Digestive system	Cardiovasc./Hemat.	Neurologic
|x| Tongue	| |.Aorta*	|xx.Brain*†
|x|.Salivary glands*	|xx.Heart*	|x| Periph. nerve*#
|x|.Esophagus*	| |.Bone marrow*	|x| Spinal cord (3 levels)*#
|x|.Stomach*	|x|.Lymph nodes*	|x|.Pituitary*
|x|.Duodenum*	|x|.Spleen*	|x| Eyes (optic n.)*#
|x|.Jejunum*	|x|.Thymus*	Glandular
|x|.Ileum*	Urogenital	|xx.Adrenals*
|x|.Cecum*	|xx.Kidneys*†	|x| Lacrimal gland#
|x|.Colon*	|x|.Urinary bladder*	|x| Mammary gland*#
|x|.Rectum*	|xx.Testes*†	|x|.Parathyroids*††
|xx.Liver*†	|x| Epididymides	|x|.Thyroids*††
| | Gall bladder*#	|x| Prostate	Other
|x|.Pancreas*	|x| Seminal vesicle	|x| Bone*#
Respiratory	|x| Ovaries*†	|x| Skeletal muscle*#
|x|.Trachea*	|x|.Uterus*	|x| Skin*#
|x|.Lung*		|x| All gross lesions and masses*
| |Nose°		
|x|Pharynx°		
| |Larynx°		

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ Weight:

The mean values of the absolute and relative organ weights are presented in Table 5. There were increases in both absolute and relative liver weights in high-dose males and in high dose females relative to the corresponding controls. The report did not present any statistical analysis. This reviewer conducted a Two-Sample-t-test, and found the increases in high dose males to be statistically significant ($p<0.001$).

TABLE 5+

Group Mean Organ Weights (Absolute and Relative)

(DATA ABSTRACTED FROM the SUBMISSION; MRID No. 50290)

Sex and Dose (mg/kg)		Brain	Heart	Liver	Kidneys	Adrenals	Testes	Final Weight (grams)
MALES								
0	Absolute	0.471	0.201	2.269	0.767	0.009	0.221	41.0
	Relative	1.149	0.490	5.534	1.871	0.022	0.539	
	S.D.	0.03+	0.04	0.86	0.15	*	0.04	6.12
25	Absolute	0.485	0.204	2.523	0.863	0.010	0.240	42.0
	Relative	1.155	0.486	6.007	2.055	0.024	0.571	
	S.D.	0.03	0.03	1.03	0.17	*	0.04	6.18
100	Absolute	0.487	0.205	2.401	0.805	0.010	0.233	42.0
	Relative	1.160	0.488	5.717	1.917	0.024	0.555	
	S.D.	0.03	0.02	0.49	0.13	*	0.03	6.34
300	Absolute	0.480	0.195	3.511	0.648	0.010	0.219	40.0
	Relative	1.200	0.488	8.778	1.620	0.025	0.548	
	S.D.	0.03	0.03	1.39	0.09	*	0.03	6.20
FEMALES								
0	Absolute	0.503	0.171	2.018	0.555	0.012		36.0
	Relative	1.397	0.475	5.606	1.542	0.033		
	S.D.	0.03	0.02	0.78	0.11	*		5.94
25	Absolute	0.483	0.172	1.877	0.571	0.015		36.0
	Relative	1.342	0.478	5.214	1.586	0.042		
	S.D.	0.05	0.04	0.41	0.11	*		5.74
100	Absolute	0.498	0.169	2.170	0.638	0.013		37.0
	Relative	1.346	0.457	5.865	1.724	0.035		
	S.D.	0.03	0.03	0.72	0.13	*		6.13
300	Absolute	0.497	0.162	2.450	0.601	0.015		35.0
	Relative	1.420	0.463	7.000	1.717	0.037		
	S.D.	0.03	0.03	0.96	0.08	*		6.85

* - Wide range of values and small numbers precluded calculating a meaningful standard deviation.

+ - THE VALUES OF S.D. Relate To Absolute Weights only, according to the Individual animal data.

b. Gross pathology

Gross pathological examination did not reveal any compound-related abnormalities.

c. Microscopic Pathology:

1) Non-neoplastic lesions:
According to the tabulated results in the report, increased incidence of non-neoplastic lesions were mostly seen in the liver and biliary system of of the high dose male mice as shown in Table 6. The increased in the incidence of hepatic regeneration was even seen in low dose males, and the increase showed a dose-reponse relationship. Some values in Tale 6 were randomly selected for validation against the individual animal data, but most of them could not be verified by the individual animal data.

TABLE 6*
Non-Neoplastic Lesions in 2,4-DP Treated and Controls
Male Mice

Dose (mg/kg):	0	25	100	300
No. of mice examined:	90	51	50	50
Hepatocellular anisocytosis				
moderate	3†	2	6	14†
marked		1		†
Hepatic regeneration	1	4	7	16
Degenerating/necrotic hepatocytes				
mild		2		9
moderate			1	1
Bile retention and/or bile granulaomas				
mild	4†	4		13†
moderate				16†
marked				1
Bile duct Duplication		1		7

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* : Data abstracted from Table 14 of the submission (MRID No. 50290).

† : These values (as reported in Table 14 of the submission) can not be verified by the individual animal data.

In addition, increased incidence of hematopoiesis was observed in mid dose males and females relative to the controls, but this was not observed in the the high dose animals.

2) Neoplastic Lesions:

According to the report, the tumor incidences in treated animals were comparable to those of the controls (Table 7).

DISCUSSION and SUMMARY:

Dietary administration of 2,4-DP acid to CD-1 mice at doses of 300 mg/kg produced significant increases in absolute and relative liver weight compared to the controls. According to the report, increases in the incidences of hepatcellular anisocytosis, of hepatic regeneration, and of degenerating/necrotic hepatocytes. In addition, increased incidences of bile retention and/or bile granulomas and of bile duct duplication were found. However, in the process of validating the tabulated histopathology data, several discrepancies were found as discussed below. These discrepancies introduced serious doubts about the validity of the report and the study.

Increased tumor incidence was not observed in treated animals relative to the controls. However, the highest dose tested (300 mg/kg) had not approached the maximum tolerated dose (MTD) because the body weight, food consumption, and survival rates were essentially all comparable to those of the controls. In addition the cause of death of the treated mice which died prior to terminal sacrifice was not related to the treatment. Based upon the reported results, the LEL for the toxicity of 2,4-DP acid was 25 mg/kg (LDT)(increased incidence of hepatic regeneration), and NOEL could not be established.

This study was previously reviewed and classified as core guideline (Tox. Doc. No. 001995). This reviewer strongly disagrees with the former classification because the study has many deficiencies which include the following:

1) The purity and chemical analysis data of the compound were not reported.

2) No explanation was given concerning how the values of the doses (i.e. mg/kg) were derived since no chemical analyses for stability and concentration of the compound in the diet were carried out.

3) Statistical analyses were not conducted.

4) Discrepancies were found in mean body weight data and in individual animal data.

5) As discussed above, the highest dose used in this study did not approached the MTD.

6) The descriptions of histopathological examination were inconsistent. For example, for the incidence of hepatic regeration four other terms such as regeratice nodules, hypertrophic nodules, islands of regenerative hepatic nodules, and small regenerative nodules were used. To this reviewer all these terms imply hyperplastic nodules.

7) This reviewer has randomly validated a few incidnece such as anisocytosis and granulomas in the liver of the control and high dose males and found errors in Table 14 of the submission (as indicated in the legend of Table 6 of this DER). Additional errors might also exist in the report. These discrepancies introduce doubts on the validity of the report. Hence, it will be valuable that the histopathology slides be reevaluated by a pathologist who is familiar with the NTP nomanclature in diagnosing pathological lesions and the data be accurately tabulated.

This study is, thus, re-classified as <u>supplementary</u>.

TABLE 7

CUMULATIVE INCIDENCE OF TUMORS

(DATA TAKEN FROM Submission; MRID No. 50290)

No. of Animals:	90	90	50	50	50	50	50	50
Dose: (mg/kg)	0		25		100		300	
Sex:	M	F	M	F	M	F	M	F
BENIGN								
Pulmonary alveologenic adenoma(s)	20	12	9	6	8	5	10	1
Harderian gland tumor	4		1	4	1		3	1
Hepatoma(s)	7		3		1	1	9	1
Thalamic glioma						1		
Hypophyseal acidophil adenoma		1		1				
Hypophyseal chromophobe adenoma		2			1			
Hypophyseal adenoma								
Uterine leiomyoma		3		2		2		1
Endometrial polyp		2		3		2		
Uterine fibroma						1		
Ovarian stromal cell tumor						1		
Ovarian luteoma		1		1				
Ovarian papillary adenoma						1		
Ovarian leiomyoma						1		
Renal tubular adenoma	1							
Pheochromocytoma	2							
Adrenocortical adenoma	1							
Transitional cell papilloma						1		
Testicular interstitial cell tumor			1					
Mammary ductal polyp						1		
Osteoma						1		2

TABLE 7 (Cont'd)

CUMULATIVE INCIDENCE OF TUMORS

(DATA TAKEN FROM submission; MRID NO. 50290)

No. of Animals:	90	90	50	50	50	50	50	50
Dose: (mg/kg)	0		25		100		300	
Sex:	M	F	M	F	M	F	M	F
MALIGNANT								
Reticulum cell sarcoma	6	5	4	6	2	2	1	4
Thymic lymphoma	1	1	1		1	2		1
Nonthymic lymphoma	2				1	1	1	
Myeloid leukemia		2	1	1	1	1	1	1
Erythrocytic leukemia				1	1	1		
Lymphocytic leukemia							1	
Leukemia, unspecified						1		
Hypophyseal chromophobe carcinoma				1				
Harderian gland adenocarcinoma			1					
Sialadenal myoepithelioma							1	
Hemangiosarcoma of jaw		1						
Mediastinal undifferentiated sarcoma					1			
Bronchiogenic adenocarcinoma		1						
Pulmonary alveologenic carcinoma			1					
Pulmonary alveologenic adenocarcinoma	1	1						
Metastatic mammary adenocarcinoma		1						
Cardiac rhabdomyosarcoma	1							
Gastric leiomyosarcoma		1						
Duodenal papillary adenocarcinoma				1				
Duodenal adenocarcinoma	2							
Jejunal cystadenocarcinoma							1	
Abdominal osteosarcoma	1							
Splenic hemangiosarcoma		1						
Renal carcinoma							1	

TABLE 7 (Cont'd)

CUMULATIVE INCIDENCE OF TUMORS

(Data TAKEN From Submission; MRID No. 50290)

No. of Animals:	90	90	50	50	50	50	50	50
Dose: (mg/kg)	0		25		100		300	
Sex:	M	F	M	F	M	F	M	F
MALIGNANT (cont.)								
Transitional cell carcinoma						1		
Uterine leiomyosarcoma		3						
Uterine carcinoma								1
Uterine undifferentiated sarcoma		1						
Uterine undifferentiated carcinoma		1						
Hepatocellular carcinoma					1			
Ovarian granulosa cell tumor		1						
Mammary adenocarcinoma		1						
Mammary adenoacanthoma						1		
Mammary cystadenoacanthoma								1
Mammary pale cell carcinoma								1
Subcutaneous liposarcoma				1				
Subcutaneous adnexal carcinoma		1						
Subcutaneous undifferentiated carcinoma		1						
Malignant thymoma							1	