19/OPP#34144

012890

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

RECEIVED

16PP

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date: October 7, 1998

MEMORANDUM

SUBJECT: **ETHOPROP:** Review of Registrant's Rebuttal to HED'sCancer Classification

TO: Kathryn Boyle (7508W)
Chemical Review Manager
Special Review and Reregistration Division

FROM: Jess Rowland, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)
and
Kit Farwell,Toxicologist
Reregistration Branch 1
Health Effects Division (7509C)

THROUGH: William Burnam
Chairman, Cancer Assessment Review Committee
Health Effects Division (7509C)

PC Code: **041101**

SUMMARY On June 25 and August 20, 1997, Health Effects Division's Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of Ethoprop and in accordance with the *1996 Draft Guidelines for Carcinogen Risk Assessment* the Committee classified Ethoprop as a **"likely"** human carcinogen. The CARC recommended a linear low-dose (Q_1*) approach for human risk characterization and extrapolation of risk should be based on the occurrence of malignant pheochromocytomas of the adrenal glands in male rats at all dose levels tested. In response to HED's classification, the Registrant provided new historical control data and arguments for re-classifying ethoprop as "not likely" to be a human carcinogen. On April 1, 1998, the CARC very carefully evaluated new data submitted by the Registrant as well as previous data regarding carcinogenicity of ethoprop. ***Ethoprop remains classified as a "likely" human carcinogen with a linear low dose (Q_1*) approach for human risk characterization.*** **The registrant need to have all adrenals in the low- and mid-dose groups of the 1992 chronic rat study examined.** The weight-of-evidence evaluated by the CARC in reaching these conclusions are presented in this memorandum.

I. BACKGROUND:

On June 25 and August 20, 1997, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Ethoprop.

Ethoprop was administered in the diet to male and female Sprague-Dawley rats at 0, 1, 60, or 400 ppm and male and female Fischer 344 rats at 0, 1, 10 or 100 ppm for 24 months as well as to male and female B6C3F1 mice at 0, 0.2, 2 or 30 ppm for 24 months. In another study with Fischer 344 rats, parental animals were fed diets containing Ethoprop at 0, 60.5, 131 or 262 ppm; after weaning, the F_1 pups were fed diets containing Ethoprop at 0, 4.5, 9.0 or 18 ppm for 12 weeks and then at 0, 49, 98 or 196 ppm for 97 weeks. The Committee concluded that the dose levels tested in the Sprague-Dawley rat study and the two Fischer 344 rat studies as well as the B6C3F1 mouse study were adequate to assess the carcinogenic potential of Ethoprop. In all four studies, the principal toxicological effects were inhibition of plasma, red blood cell and/or brain cholinesterase activity as well as decreases in body weight gains. The degree of cholinesterase inhibition observed at most doses was considered to constitute "excessive" toxicity in the rats; however, the absence of clinical cholinergic signs of toxicity along with little, if any, frank pathology and increased or comparable survival in treated rats was inconsistent.

In accordance with the Agency's *Proposed Guidelines for Carcinogen Risk Assessment (April 10, 1996)*, the Committee classified Ethoprop as a **"likely"** human carcinogen. This classification is based on the following factors:

(i) presence of a rare and life-threatening (malignant) tumor (pheochromocytoma of the adrenal glands) in male Sprague -Dawley rats at the low dose in the absence of cholinesterase inhibition;

(ii) occurrence of another type of tumor (C-cell carcinomas of the thyroid glands) in male rats in two strains (Sprague-Dawley and Fischer 344) in three different studies at doses that did cause cholinesterase inhibition; and

(iii) evidence of clastogenicity *in vitro* mutagenicity testing.

The Committee recommended a linear low-dose (Q_1*) approach for human risk characterization and extrapolation of risk should be based on the occurrence of malignant pheochromocytomas of the adrenal glands in male rats at all dose levels tested. The Committee recommended this extrapolation based on the (i) lack of mode of action, (ii) evidence of carcionogenicity [occurrence of other tumor types (C-cell carcinomas of the thyroid glands) at doses that caused cholinesterase inhibition], and (iii) confirmation of clastogenic activity in mutagenicity testing.

In response to the Agency's classification of ethoprop, the registrant provided new historical control data and arguments for re-classifying ethoprop as "not likely" to be a human carcinogen. The CARC reviewed the additional data on April 1, 1998. The Committee's conclusions of this meeting are discussed in this report.

II. REVIEW OF REGISTRANT'S REBUTTAL

1. Malignant Adrenal Pheochromocytomas in Male Sprague-Dawley Rats

Reference: Combined Chronic Toxicity/Carcinogenicity Study in Sprague Dawley Rats (MRID 42530201).

(i) HED's Assessment

The CARC's primary concern was the occurrence of malignant pheochromocytomas of the adrenal gland in male Sprague-Dawley rats, a rare life-threatening tumor in this species. This tumor type was seen at all dose levels tested. The incidence at the high dose (400 ppm) reached pair-wise statistical significance when compared to concurrent controls and exceeded the historical control range. Malignant pheochromocytomas were also seen at the mid-(60 ppm) and low-(1 ppm) dose groups. However, since the adrenals at the low- and mid-dose groups were examined only in rats that died or were sacrificed moribund, the true dose-responsive nature of the tumor incidence at these doses could not be ascertained. The Committee noted that in contrast to the mid-and high-dose groups where tumors were seen in the presence of cholinesterase inhibition, at the low-dose, tumors were seen in the absence of cholinesterase inhibition (Cancer Assessment Document, dated October 2, 1997).

As shown in Table 1, male rats at the high dose (400 ppm) had statistically increased malignant adrenal pheochromocytomas and decreased benign and combined pheochromocytomas compared to controls. The two-year survival rate in high-dose males was twice that of controls (58% in the high-dose group vs 29% in controls.

Table 1. Adrenal Tumors and Mortality in Male Sprague Dawley Rats (MRID No. 42530201).

	DOSE (ppm)			
	0	1	60	400
Mortality Rate (weeks 1-106)	50/70 (71%)	42/70 (60%)[n]	42/70 (60%)[n]	**30/71 (42%)**[n]**
Tumor Type / Incidence				
Benign Pheochromocytomas	14/49 (29%)[n]	7/26[a]	7/28[a]	5/61 (8%)[n]
Malignant Pheochromocytomas	0/41(0%)**	2/16[a]	2/18[a]	**5/60 (8%)****
Combined Pheochromocytomas	14/49 (29%)[n]	8/26[a]	9/28[a]	10/61 (16%)[n]

[n] Negative trend or change from control. [a] Not all animals examined. ** $p<0.01$.

3916

(ii) **Registrant's Rebuttal**

According to the Registrant (Rhone-Poulenc) pathologist, adrenal pheochromocytomas are common, age-related tumors; benign pheochromocytomas progress to malignancy. The increase in malignant pheochromocytomas in high-dose males was attributed to the two-fold increased survival in that group which allowed more time for benign adrenal tumors to progress to malignancies.

Logistic regression analysis found high dose malignant pheochromocytomas were not statistically different than controls (p=0.83). The RP report says that the Peto Prevalence Test accounts for survival differences but is sensitive to the time period intervals selected. The Registrant submitted new historical control data since the study date. Historical incidence at Hazleton (now Covance) laboratory from 1990-1995 for malignant adrenal pheochromocytomas is 5.2%, range of 0-10% (all death codes), compared to an incidence of 8% in the present study (see attached Appendix).

(iii) **HED's Response**

The Committee's primary concern is still the occurrence of malignant adrenal pheochromocytomas which was seen at all dose levels tested. Incidence at the high-dose (400 ppm) reached pair-wise statistical significance when compared to concurrent controls. Malignant pheochromocytomas were also seen at the low- (1 ppm) and mid-dose groups (60 ppm). However, not all adrenals in the low- and mid-dose group were examined, so the true dose-responsive nature of tumor incidence could not be determined.

Malignant pheochromocytomas exceeded the historical control range for the period of approximately 5 years preceding this study. However, the registrant submitted new historical control data from the testing lab for approximately 5 years after the study. In the new historical control data, pheochromocytomas in the present study had a similar incidence for 1 study while another study had an incidence above the current study. One study had decreased incidence compared to the present study and another study had zero malignant pheochromocytomas.

The criteria for distinguishing between benign and malignant pheochromocytomas has changed over the years. The present criteria for classification of malignancy is tissue invasion or metastasis. It could not be determined which criteria were used in the 1992 study and which criteria were used in the historical control studies. **The registrant needs to describe the criteria used for classification of pheochromocytomas in the historical control studies.**

Malignant adrenal pheochromocytomas are classified as "uncommon" tumors by the Society of Toxicologic Pathologists, but should not be described as "life-threatening" as mentioned in the preceding CPR document (5/9 animals with these tumors survived to study termination). Benign pheochromocytomas cannot be stated as progressing to malignancy, according to HED consulting pathologist, Dr. Luke Brennake.

In additon, in this study there were fewer surviving control animals compared to all male treatment groups at study termination (20, 28, 28, and 41 survivors in control, low-, mid-, and high-dose groups respectively). The Registrant argued that increased survival in the high-dose group allowed more time for benign pheochromocytomas to progress to malignancy. However, this argument was rejected because benign pheochromocytomas cannot be stated as progressing to malignancy.

Although the Registrant submitted data showing that the increase in malignant pheochromocytomas was not significantly increased using logistic regression analysis, HED uses the Peto prevalence test which also accounts for differential survival among groups and is more sensitive than logistic regression analysis.

The Committee evaluated doses tested study and concluded that dosing was excessive and was close to a lethal dose based on the following fators:

1) The high dose had to be reduced from 600 ppm to 400 ppm after 2 weeks of dosing due to excessive toxicity in females (tremor, ataxia, and 2 deaths).

2) Brain ChE activity in 400 ppm males was decreased -64% compared to controls at study termination.

3) There were body weight decrements of approximately -20% compared to controls during the first half of the study.

4) Neurotoxicity was noted in a subchronic neurotoxicity study (MRID 43442401) at the same dose as the high dose in the 1992 chronic rat study (400 ppm). Neurotoxicity included cholinergic signs, decreased analgesic response, decreased motor activity, and decreased hindlimb grip strength. These signs of neurotoxicity are more likely to be detected in the neurotoxicity study than in a chronic study.

5) The high-dose group of 400 ppm was equivalent to 20 mg/kg/day. This dose is approximately 2/3 of the LD_{50} oral dose for ethoprop (32.8 mg/kg).

6) Ethoprop has a steep dose-response curve with death occurring at dose levels slightly above those causing clinical signs.

2. Thyroid C- Cell Carcinomas in Male Spraague Dawley Rats

Reference: Combined Chronic Toxicity/Carcinogenicity Study in Sprague Dawley Rats (MRID 42530201).

(i) HED's Assessment

The CARC also had concern for the occurrence of C-cell tumors of the thyroid glands in male Sprague-Dawley rats referenced above as well as in two different studies in male Fisher 344 rats.

As shown in Table 2, the incidence of **C-cell carcinomas** at the high dose (400 ppm) showed a positive trend, reached pair-wise significance when compared to controls, and exceeded the historical control range. In Fischer 344 rats, while positive trends were seen for C-cell adenomas, carcinomas, and combined adenomas/carcinomas, there was a non-statistically significant increase in C-cell carcinomas at the high dose (100 ppm) in males when compared to none in the concurrent controls. The increase in C-cell carcinomas in this strain of rats is supportive of the same target organ/tumor type in the Sprague-Dawley rats.

Table 2. Thyroid C-Cell Tumors in Male Sprague-Dawley Rats (MRID No. 42530201).

Tumor Type / Incidence	DOSE (ppm)			
	0	1	60	400
C-Cell Adenomas	8/66 (12%)	6/67 (9%)[n]	9/67 (13%)	12/68 (18%)
C-Cell Carcinomas	0/61 (0%)*	0/63 (0%)	1/64 (2%)	**3/66 (5%)***
Combined C-Cell Tumors	8/66 (12%)	6/67 (9%)[n]	10/67 (15%)	15/68 (22%)

[n]Negative trend. * $p<0.05$ ** $p<0.01$. Tumor rates exclude rats dying before first tumor.

(ii) Registrant's Rebuttal

The Registrant stated that the increase in thyroid C-cell carcinomas is not statistically significant by logistic regression analysis. Increased thyroid C-cell carcinomas in high-dose males was due to increased two-year survival in that group (58% in the high-dose group vs 29% in controls).

The Registrant also contends that comparison to historical control data is not always appropriate with increased survival because the longer-lived animals in the 1992 study died from different causes than rats in the historical database.

3. Thyroid Follicular Cell Adenomas in Male Sprague Dawley Rats

Reference: Chronic Toxicity/Carcinogenicity Study in SD Rats (MRID 42530201).

(i) HED's Assessment

The CARC had lesser concern for this tumor type since combined adenomas/carcinomas had only borderline significance at the high dose (Table 3), but was seen as supporting evidence for the thyroid being a target organ for ethoprop-induced carcinogenicity.

6916

Table 3. Thyroid Follicular Cell Tumors in Male Sprague Dawley Rats (MRID No. 42530201).

Tumor Type / Incidence	DOSE (ppm)			
	0	1	60	400
Follicular Cell Adenomas	0/53 (0%)	**4/56 (7%)***	**4/56 (7%)***	**5/63 (8%)***
Follicular Cell Carcinomas	1/34 (3%)	0/31 (0%)	1/36 (3%)	1/51 (2%)
Combined Follicular Cell Tumors	1/53 (2%)	4/56 (7%)	5/56 (9%)	6/63 (10%)

4. Thyroid C-Cell Tumors in Male F344 Rats

Reference: Combined Chronic Toxicity/Carcinogenicity - 1985 (MRID No. 40291801) Combined Chronic Toxicity/Carcinogenicity *in utero* study - 1983 (MRID No. 00138636).

(i) HED's Assessment

In the 1985 study (MRID No. 40291801) ethoprop was administered in the diet and in the 1983 study (MRID No. 00138636) rats were exposed to ethoprop *in utero*, during lactation and then by diets. Both of these studies were classified Core supplementary by the HED Reference Dose Peer Review Committee. The 1985 feeding study appeared upgradeable to the reviewer if requested data had been submitted. The RfD Committee did not review the 1983 chronic/carcinogenicity *in utero* study and said it was superseded by the 1992 study.

Table 4. Thyroid C-Cell Tumors in Male F344 Rats (MRID No.40291801).

Tumor Type / Incidence	DOSE (ppm)			
	0	1	10	100
C-Cell Adenomas	8/49 (16%)*	5/48 (10%)[n]	5/50 (10%)[n]	12/50 (24%)
C-Cell Carcinomas	0/49 (0%)*	0/48 (0%)	1/50 (2%)	3/50 (6%)
C-Cell Combined Tumors	8/49 (16%)**	5/48 (10%)[n]	6/50 (12%)[n]	15/50 (30%)

7816

As shown above in Table 4, male rats in the 1985 feeding study (MRID No. 40291801) exhibited a statistically significantly increasing trend for thyroid C-cell adenomas, carcinomas, and combined tumors.

In the 1983 *in utero* study (MRID No. 00138636), males had significant increasing trends for thyroid C-cell adenomas as well by pair wise comparison of the high-dose group with controls (Table 5).

Table 5.Thyroid C-Cell Adenomas in Male F344 Rats (MRID 00138636)

	DOSE (ppm)			
	0	49	98	196
C-Cell Adenomas	2/46 (4%)*	4/43 (9%)	1/41 (2%)[n]	10/40 (25%)*

* $p<0.05$ ** $p<0.01$. Tumor rates exclude rats dying before first tumor.
[n]Negative trend or change from control.

(ii) Registrant's Response

The Registrant stated that that thyroid C-cell tumors in the 1985 study should be discounted because there is a positive trend but no significance for pair-wise comparisons. and the the thyroid C-cell adenomas in the 1983 report should be discounted because carcinomas were not increased with treatment.

The Registrant contends that neither the 1983 study nor the 1985 study should be compared to the 1992 study because no historical control data is available for either study and the studies were conducted a decade apart when the historical control data would have changed. Also different sampling techniques and diagnostic criteria were used in the different studies. Additonally, the Registrant stated that the 1983 study by Biosafety Research Center, Japan, was not conducted according to Good Laboratory Practices.

(iii) HED's Response

The Committee had lesser concern for thyroid C-cell and follicular tumors which occurred in several chronic rat studies. Both of these tumor types are common.

Thyroid C-cell carcinomas in the 1992 rat study showed an increasing trend as well as significant pair-wise comparison of the high-dose male group with controls (3/61 in the high-dose group compared to 0/61 in controls). Thyroid follicular cell adenomas in the same study were increased by pair-wise comparison for all treatment groups. The Committee felt that these were small increases and that the maximum tolerated dose had been exceeded for the reasons listed above.

8916

Thyroid C-cell adenomas and carcinomas showed increasing trends in the 1985 rat study. Again, the Committee felt that these were small increases. For further details, refer to the Cancer Assessment Document dated October 2, 1997.

Thyroid C-cell adenomas in the 1983 rat *in utero* study showed an increasing trend as well as significance by pair-wise comparison of the high-dose group with controls. For further details, refer to the Cancer Assessment Document dated October 2, 1997.

III. SUMMARY OF MUTAGENICITY TESTING WITH ETHOPROP:

Ethoprop is an *in vitro* clastogen with metabolic activation required for genotoxicity. Due to severe toxicity, it could not be determined whether ethoprop is an *in vivo* clastogen. Additional mutagenicity testing is not required due to the limitations posed by toxicity. Both pre-1991 and current mutagenicity initial testing battery guidelines are satisfied. Results are summarized in Table 6.

Table 6. Results of the Mutagenicity Assays.

Assay Type	Results
Salmonella typhimurium reverse gene mutation assay (MRID No.00160180)	Negative
Chinese hamster ovary (CHO) cell HGPRT gene mutation assay (MRID No.00160181)	Negative
Mouse lymphoma L5178Y forward gene mutation assay (MRID 44065001)	Negative
In vitro CHO cell chromosome aberration assay (MRID 00160183)	Postive with S9 activation
In vivo bone marrow cytogenetic assay (MRID No.41211202)	Negative in SD rats. No apparent interaction with target tissue; severe toxicity at the highest dose.
Rat dominant lethal assay (MRID 40386901)	Negative in SD rats. No apparent interaction with target tissue; severe toxicity at the highest dose.
In vitro unscheduled DNA synthesis in primary rat hepatocytes (MRID 00160182)	Negative
In vitro unscheduled DNA synthesis in primary rat hepatocytes (MRID 44038702)	Negative
In vitro CHO cell sister chromatid exchange assay (MRID 00160184)	Positive with S9 activation

9916

V. CONCLUSIONS:

The CARC very carefully evaluated new data submitted by the registrant as well as previous data regarding carcinogenicity of ethoprop. The concerns of the CARC regarding malignant adrenal pheochromocytomas were mitigated somewhat by the new historical control data as well as evidence that rats in the high-dose group had been tested at an excessive dose that was very close to a lethal dose.

However, not all adrenals in the low- and mid-dose groups in the 1992 rat study were examined. Until these adrenals are all examined, there is insufficient evidence to change the carcinogenicity classification of ethoprop. **Ethoprop remains classified as a "likely" human carcinogen with a linear low dose (Q_1*) extrapolation approach for human risk characterization. The registrant need to have all adrenals in the low- and mid-dose groups of the 1992 chronic rat study examined.**

VI. BIBLIOGRAPHY

MRID No.	CITATION
NA	Ethoprop - Report of the Cancer Assessment Review Committee (dated 10/2/97).
MRID 42530201	104-Week Combined Chronic Toxicity and Carcinogenicity Study with Ethoprop in Rats (1992).
MRID 40291801	Lifetime Dietary Toxicity and Oncogenicity Study in Rats (1985).
MRID 00138636.	Evaluation of the Chronic Toxicity and Oncogenic Potential of Ethoprop in Fischer 344 Rats (1983).
MRID Nos 40356301 and 43326001	Chronic Feeding and Oncogenicity Studies in Mice with Ethoprop (1984).
MRID 43442401	13-Week Dietary Neurotoxicity Study with Ethoprop in Rats (1994).

The following citations are not available electronically. See the file copy.

Attached is historical control data for adrenal pheochromocytomas and thyroid C-cell tumors in Crl:CD BR rat dietary studies from Hazleton Laboratory (now Covance), 1990-1995.

10816

COVANCE
THE DEVELOPMENT SERVICES COMPANY

Covance Laboratories Inc
P.O. Box 7545
Madison, Wisconsin 53707-7545
Packages: 3301 Kinsman Boulevard
Madison, Wisconsin 53704
Tel: 608/241-4471
Fax: 608/241-7227

HISTORICAL HISTOPATHOLOGY CONTROL DATA
Rat, Crl:CD BR, Dietary
Study Duration: 104 Weeks
Terminal Sacrifice

Male Animals HDBS Study Number	86DE	180DE	185DE	186DE	TOTAL
ADRENALS Number examined	28	22	7	19	76
Hyperplasia, Medullary Cell	7	3	1	1	12
Percent (%)	25.0	13.6	14.3	5.3	15.8
B-Pheochromocytoma	3	5	0	3	11
Percent (%)	10.7	22.7	0.0	15.8	14.5
M-Pheochromacytoma	0	0	1	2	3
Percent (%)	0.0	0.0	14.3	10.5	3.9
Proliferative Change	10	8	2	4	26
Percent (%)	35.7	36.4	28.6	21.1	34.2
THYROID Number examined	28	22	7	19	76
Hyperplasia, C-Cell	11	10	4	3	28
Percent (%)	39.3	45.5	57.1	15.8	36.8
B-Adenoma, C-Cell	9	2	1	3	15
Percent (%)	32.1	9.1	14.3	15.8	19.7
M-Carcinoma, C-Cell	1	0	0	0	1
Percent (%)	3.6	0.0	0.0	0.0	1.3
Proliferative Change	21	12	5	6	44
Percent (%)	75.0	54.5	71.4	31.6	57.9

February 5, 1998

COVANCE
THE DEVELOPMENT SERVICES COMPANY

Covance Laboratories Inc.
P.O. Box 7545
Madison, Wisconsin 53707-7545
Packages: 3301 Kinsman Boulevard
Madison, Wisconsin 53704
Tel: 608/241-4471
Fax: 608/241-7227

HISTORICAL HISTOPATHOLOGY CONTROL DATA
Rat, Crl:CD BR, Dietary
Study Duration: 104 Weeks
All Death Codes

Male Animals HDBS Study Number	86DE	180DE	185DE	186DE	TOTAL
ADRENALS Number examined	50	60	60	60	230
Hyperplasia, Medullary Cell	9	6	6	6	27
Percent (%)	18.0	10.0	10.0	10.0	11.7
B-Pheochromocytoma	6	8	3	6	23
Percent (%)	12.0	13.3	5.0	10.0	10.0
M-Pheochromacytoma	0	6	1	5	12
Percent (%)	0.0	10.0	1.7	8.3	5.2
Proliferative Change	15	20	10	17	72
Percent (%)	30.0	33.3	16.7	28.3	31.3
THYROID Number examined	50	60	60	60	230
Hyperplasia, C-Cell	12	10	10	7	39
Percent (%)	24.0	16.7	16.7	11.7	17.0
B-Adenoma, C-Cell	12	9	1	4	26
Percent (%)	24.0	15.0	1.7	6.7	11.3
M-Carcinoma, C-Cell	1	0	0	0	1
Percent (%)	2.0	0.0	0.0	0.0	0.4
Proliferative Change	25	19	11	11	66
Percent (%)	50.0	31.7	18.3	18.3	28.7

February 5, 1998

Spontaneous Neoplastic Lesions and Selected Non-neoplastic Lesions in the Crl:CD [illegible]

February, 1992

Charles River
LABORATORIES

TABLE 5a (Continued)
NEOPLASMS
24 MONTH STUDIES
MALE CD® RATS

LOCATION & TUMOR	# groups in which organ examined	total # lesions	percent of total	# groups using this diagnosis	minimum % found	maximum % found
THYROID GLAND	19					
follicular cell adenoma		69	5.55	17	1.1	25.7
follicular cell carcinoma		16	1.29	12	1.0	6.0
C-cell adenoma		79	6.35	17	1.0	17.4
C-cell carcinoma		29	2.33	13	1.1	7.0
PARATHYROID GLAND	19					
adenoma (B)		15	1.28	11	1.4	7.4
adenocarcinoma		1	0.09	1	-	2.7
ADRENAL GLAND	19					
cortical adenoma (B)		36	2.88	15	1.4	16.4
cortical carcinoma		5	0.40	5	1.4	2.0
pheochromocytoma (B)		188	15.05	19	4.0	30.0
pheochromocytoma (M)		24	1.92	12	1.6	8.6
ganglioneuroma		2	0.16	2	1.7	2.0
NERVOUS SYSTEM						
BRAIN	19					
glioma (B)		1	0.08	1	-	1.4
glioma (M)		4	0.32	2	3.3	4.0
astrocytoma (B)		5	0.40	3	2.0	4.3
astrocytoma (M)		11	0.88	6	1.0	5.7
astrocytoma (M), spinal cord		3	0.24	2	2.0	2.0
granular cell tumor (B)		2	0.16	2	1.4	2.0
granular cell tumor (M)		2	0.16	2	1.3	1.4
adenocarcinoma		4	0.32	2	2.1	6.1
sarcoma, spinal chord		1	0.08	1	-	2.0
PERIPHERAL NERVES	16					
neurofibroma (M)		1	0.09	1	-	1.8
neurinoma, thorax		1	0.09	1	-	1.0
BODY CAVITIES						
ABDOMINAL CAVITY	19					
lipoma		2	0.16	2	1.4	1.8
liposarcoma		2	0.16	2	1.1	1.4
fibrosarcoma, mesentery		1	0.08	1	-	1.4
hemangioma, mesentery		1	0.08	1	-	1.4
fibrous histiocytoma (M), mesentery-omentum		1	0.08	1	-	2.0
mesothelioma (B), abdomen		1	0.08	1	-	1.4
carcinoma (M), seminal vesicle		1	0.08	1	-	1.4
THORACIC CAVITY	19					
liposarcoma		2	0.16	1	-	2.2
hibernoma		1	0.08	1	-	1.1
ORAL CAVITY	19					
fibrosarcoma, gingiva		1	0.08	1	-	1.4
squamous cell carcinoma, mouth		1	0.08	1	2.0	2.0

NEOPLASMS
12-13 MONTH STUDIES
MALE CD® RATS

LOCATION & TUMOR	# groups tissue examined	total # lesions	overall total	# groups using this diagnosis	minimum % found	maximum % found
INTEGUMENTARY SYSTEM						
SKIN	19					
papilloma		1	0.32	1	-	5.0
keratoacanthoma		4	1.29	4	5.0	10.0
pilomatrixoma (B)		2	0.65	2	3.7	10.0
myxofibroma (B)		1	0.32	1	-	5.6
sebaceous gland carcinoma		1	0.32	1	-	5.0
CIRCULATORY SYSTEM						
HEART	19					
endocardial sarcoma		1	0.32	1	-	6.7
DIGESTIVE SYSTEM						
LIVER	19					
hepatocellular carcinoma		1	0.32	1	-	5.3
ENDOCRINE SYSTEM						
PANCREAS (ENDOCRINE)	19					
islet cell adenoma		2	0.65	2	4.3	10.0
PITUITARY GLAND	19					
adenoma, pars distalis		37	12.09	14	5.0	40.0
carcinoma, pars distalis		3	0.98	1	-	15.8
THYROID GLAND	19					
follicular cell adenoma		1	0.32	1	-	5.3
C-cell adenoma		2	0.65	2	3.6	6.7
ADRENAL GLAND	19					
cortical adenoma (B)		4	1.30	4	5.0	10.0
pheochromocytoma (B)		2	0.65	2	10.0	10.0
NERVOUS SYSTEM						
BRAIN	19					
ependymoma		1	0.32	1	-	5.6

15816

24 MONTH STUDIES
MALE CD® RATS

LOCATION & TUMOR	# groups in which organ examined	total # lesions	percent of total	# groups using this diagnosis	minimum % found	maximum % found
LIVER	19					
nodular hepatocellular proliferation		9	0.72	2	8.0	10.2
hepatocellular adenoma		53	4.21	18	1.3	18.2
hepatocellular carcinoma		33	2.62	12	1.1	9.1
cholangioma		1	0.08	1	-	1.4
cholangiocellular carcinoma		2	0.16	2	1.0	2.0
carcinosarcoma		1	0.08	1	-	2.0
PANCREAS (EXOCRINE)	19					
acinar cell adenoma		7	0.56	7	1.3	2.0
sarcoma (NOS)		1	0.08	1	-	1.8
URINARY SYSTEM						
KIDNEY	19					
renal cell adenoma		3	0.24	3	1.4	2.1
renal adenocarcinoma		4	0.32	4	1.0	2.0
transitional cell carcinoma		2	0.16	2	1.4	2.0
hemangiosarcoma		1	0.08	1	-	2.1
lipoma		1	0.08	1	-	1.3
liposarcoma		1	0.08	1	-	2.1
lipomatous tumour (M)		1	0.08	1	-	1.0
mixed cell tumor (M)		3	0.24	2	2.0	3.0
mixed mesenchymal tumor (NOS)		1	0.08	1	-	1.4
URINARY BLADDER	19					
transitional cell papilloma		1	0.08	1	-	1.0
transitional cell carcinoma		3	0.24	3	1.4	1.5
mesothelioma		1	0.08	1	-	1.0
REPRODUCTIVE SYSTEM						
TESTIS	19					
interstitial (leydig) cell tumor (B)		59	4.68	18	1.4	10.0
interstitial cell tumor (M)		1	0.08	1	-	1.4
mesothelioma (M)		2	0.16	2	1.0	1.4
PROSTATE	19					
carcinoma (M)		3	0.24	3	1.0	1.8
lipoma		1	0.08	1	-	1.4
mesothelioma (M)		1	0.08	1	-	1.0
ENDOCRINE SYSTEM						
PANCREAS (ENDOCRINE)	19					
islet cell adenoma		103	8.29	17	2.9	24.0
islet cell carcinoma		25	2.01	10	1.6	8.2
mesothelioma		1	0.08	1	-	1.0
PITUITARY GLAND	19					
adenoma, pars intermedia		4	0.32	2	1.0	4.9
adenoma, pars distalis		750	60.68	19	37.1	81.3
carcinoma,						
pars distalis		79	6.39	10	1.0	33.3
craniopharyngioma		1	0.08	1	-	1.9
hemangioma		1	0.08	1	-	1.9