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CASWELL FILE

069003

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

JUL 15 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg.No. 10308-1 - Tetramethrin: Review of mouse oncogenicity study. Return of study and request for additional information to complete review.

TOX CHEM No. 844
TOX Project No. 1753
Record No. 173893

FROM: John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Arturo Castillo, PM #17
Registration Division (TS-767)

THRU: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

EBudd 7/13/86

7/14/86

The mouse oncogenicity study with the insecticide tetramethrin (Neopynamin) was sent to the Dynamac Corporation for review and following a cursory review has been returned to Toxicology Branch (TB) because of deficiencies in the reporting of the study data (see Dynamac letter, dated 6/24/86, attached). The study sponsor (Sumitomo, Ltd.) is requested to provide the following information to assist in an efficient review of the study.

1. Revised Summary Incidence Table. The table should contain the combined results of the mice sacrificed at termination, interim sacrifices and the unscheduled deaths. The Table must retain the information on the exact number of mice for which each tissue/organ was examined and the number and type of each lesion noted.

   The revised Summary Incidence Table should be arranged such that neoplasms are listed first and the nonneoplastic lesions are listed as a separate group. Refer to sample Summary Incidence Table attached.

[Note: The study report currently has 4 "Histopathology Incidence Summary" tables containing the above information that should be revised or combined to satisfy the above request.]

2. The study report must include an Individual Histopathology Incidence Table which details which individual animals have which lesions. Refer to the sample of the Individual Histopathology Incidence Table attached. For each animal and tissue, it should be clear as to whether or not the specific tissue was examined. Lesions should be graded where possible.

3. A summary Table listing the organ weight data for individual animals. The individual organ weights are requested by the contract reviewer to do statistical analysis of these data.

4. Separate Table listing the neoplasms by animal number, days on study at time of death and cause of death (planned sacrifice or unscheduled death).

5. TB is concerned with the high incidences of the hepatocellular adenomas in the concurrent control group(s) in this study which are considerably higher than the historical control data for this strain from the Hazleton Laboratory. The reported incidences are, however, within or slightly in excess of the range reported for this strain in the literature (Goodman et al, Handbook of Carcinogen Testing, in press).

   The testing laboratory is requested to provide as best an explanation as possible for the sudden increase in spontaneous liver adenomas in this strain of mouse relative to historical control data from this laboratory. Data on control groups from studies run at approximately the same time or later with this same strain of mouse and preferably from the same supplier would be very helpful in this regard. Information on the individual pathologists employed at Hazleton over the years that the B6C3F1 mouse data were generated and the criteria used in diagnosing adenomas will also be helpful.

*6. Historical control data for incidences of Harderian gland adenomas/carcinomas.

*7. Historical control data for hemangiomas and hemangiosarcomas including but not limited to the spleen

*See next page for footnote.

*8. Historical control data for ~~the~~ neoplastic and nonneoplastic lesions of the pituitary, adrenal and thyroid glands.

*Historical control data for the lesion types listed above from the same strain of mouse used in the study with tetramethrin submitted in response to this request should consist of at least the following:

i. Data from animals from the same supplier (if possible).

ii. Data from all available mouse oncogenicity studies conducted at the testing facility with this strain of mouse.

iii. The data from each individual study should be submitted. Results from the different studies should not be pooled and presented in a summary form of the pooled data only, although a pooled summary table may also be presented.

iv. For each individual study, the following information should be provided:

a. Strain and source of experimental animals.

b. Laboratory performing the study.

c. Dates of initiation and termination of each study.

d. Number of male and female animals in the control group and the number of animals for which the tissue/organ was <u>actually</u> examined histologically.

CASWELL FILE

DYNAMAC CORPORATION

Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, Maryland 20852
Telephone: 301-468-2500
Telex: 248838

June 24, 1986

Mr. Edwin Budd
Hazard Evaluation Division
U.S. EPA - Toxicology Branch
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Dear Ed:

As requested, the CBI for Tetramethrin (EPA Accession Nos. 262778-262788) is being returned.

After examination of the study, several reporting deficiencies were noted. There were no composite tables of histologic findings with animal numbers; therefore tumors for each individual animal could not be determined without reviewing all individual pathology sheets. For example, it could not be determined how many animals in each group had both hepatocellular adenoma and carcinoma. Summary tables of histopathology were presented including number of tissues examined but neoplastic and non-neoplastic lesions were not separated. Also to determine neoplasm incidence, summary tables for animals that died and animals sacrificed by design had to be combined. Neoplasms were not listed by animal number. Organ weight data for individual animals were not summarized; however, summary tables with means and standard deviations were provided. Since a LOEL and NOEL are based on weights of endocrine organs, these data are necessary to check statistics and spot outlying values.

Historical control incidence for Harderian gland adenomas, and hemangiosarcomas of the spleen would be useful for evaluating the study. Also it was noted that the concurrent control incidence of hepatocellular adenoma is considerably higher than normally found for the strain of mouse used and available historical incidence of the testing laboratory.

Thank you for requesting the required data.

Sincerely,

William L. McLellan

William L. McLellan
Senior Staff Scientist

Task #4

Enviro Control Division

SAMPLE SHEET

EVERY PATHOLOGY REPORT SHOULD HAVE INDIVIDUAL:
STOPATHOLOGY INCIDENCE TABLE

Group 1

Male Mice
Scheduled Sacrifices

ANIMAL NUMBER	16845-6	16845-7	16845-8	16845-9	16846-0	16846-1	16846-2	16846-3	16846-4	16846-5	16846-6	16846-7	16846-8	16846-9	16847-0	16847-1	16847-2	16847-3	16847-4
LUNG		X				X	X				X			X	X		X	X	X
Alveolar/Bronchiolar Carcinoma																			
Malignant Lymphoma																			
Malignant Lymphoma, Undifferentiated																			
Alveolar/Bronchiolar Adenoma								P		P									
Carcinoma, Metastatic																			
Granulocytic Leukemia																			
Sarcoma, Metastatic					P														
Multifocal Pleuritis																			
Multifocal Pneumonitis			2																
Alveolar Macrophages, Pigmented																1			
Focal Alveolar/Bronchiolar Hyperplasia																			
Congestion																			
Focal Hemorrhage									3										
Alveolar Macrophages																			
Foci of Foamy Macrophages																			
Leukocytosis																			
Peribronchial/Vascular Mononuclear Cells	1		1	1								2	1			1			
Alveolar Proteinosis																			
Multifocal Alveolar-Bronchiolitis	1															1			

SAMPLE SHEET

EVERY PATHOLOGY REPORT SHOULD HAVE:
SUMMARY INCIDENCE TABLE

e Mice

	Group 1			Group 5			Group 6			Group 7		
	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total
NO. EXAMINED)	(43)	(7)	(50)	(42)	(8)	(50)	(38)	(12)	(50)	(39)	(11)	(50)
eolar/Bronchiolar Carcinoma	2		2	2		2	2		2	3		
gnant Lymphoma					1	1		4	4		1	1
gnant Lymphoma, Undifferentiated		2	2				1		1		1	1
eolar/Bronchiolar Adenoma	3		3	3		3	5	2	7	4		4
inoma, Metastatic	1	1	2		1	1		2	2			
ulocytic Leukemia					1	1						
oma, Metastatic												
ifocal Pleuritis							1		1	3		3
ifocal Pneumonitis	5		5	2		2	4		4	3		3
eolar Macrophages, Pigmented	7		7	4		4				1	1	2
l Alveolar/Bronchiolar												
perplasia	2		2	2		2	2		2	1		1
estion	2	2	4	4	5	9	3	5	8	3	8	11
l Hemorrhage				2		2	1		1	1		1
olar Macrophages	2		2	2		2	2		2	1		1
of Foamy Macrophages	4		4	3		3				2		2
ocytosis				1	2	3					3	3

CASWELL FILE

DYNAMAC CORPORATION

Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, Maryland 20852
Telephone: 301-468-2500
Telex: 248838

July 9, 1986

Ms. Caroline Gordon
Hazard Evaluation Division - Room 720 - CM
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, Virginia 22202

Dear Ms. Gordon:

Per Edwin Budd's request, enclosed is Hazleton's Representative Historical Control Data.

If you have any questions regarding these data, please call.

Sincerely,

Sharon M Ambrose

Sharon M. Ambrose
Asst. Program Manager

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE, VIENNA, VIRGINIA 22180, U S A

REPRESENTATIVE HISTORICAL CONTROL DATA

PART 12

NEOPLASIA IN UNTREATED B6C3F1 MICE

HAZLETON LABORATORIES AMERICA, INC.
SUMMARY OF NEOPLASIA IN UNTREATED CONTROL B6C3F1 MICE

THE FINDINGS PRESENTED IN THIS SUMMARY ARE FROM UNTREATED CONTROL MICE INCLUDING FOUND DEAD, MORIBUND SACRIFICE AND TERMINAL SACRIFICE (WEEKS 78-105) ANIMALS.

THE TERM 'POSITIVE TOTALS' REPRESENTS THE TOTAL NUMBER OF POSITIVE FINDINGS FROM STUDIES WHERE THERE WERE ONE OR MORE OCCURRENCES OF THE INDICATED NEOPLASM IN EACH SEX. THE DATA FROM THESE STUDIES, INCLUDING THE NUMBER OF TISSUES EXAMINED, ARE PRESENTED.

THE TERM 'OVERALL TOTALS' REPEATS THE TOTAL NUMBER OF POSITIVE FINDINGS AND ALSO PRESENTS THE TOTAL NUMBER OF TISSUES OBSERVED FROM ALL QUALIFYING STUDIES, THAT IS, THOSE STUDIES WITH POSITIVE AS WELL AS NEGATIVE FINDINGS.

WHEN POSITIVE FINDINGS ARE LISTED FOR TISSUE MASS, OTHER LESIONS, MULTIPLE ORGANS, OR OTHER NON-PROTOCOL TISSUES, THE TOTAL NUMBER OF TISSUES EXAMINED REPRESENTS THE TOTAL NUMBER OF ANIMALS EXAMINED AT THAT INTERVAL OR THE TOTAL NUMBER OF ANIMALS ON STUDY, AS APPROPRIATE.

'OVERALL PERCENT' IS THEN CALCULATED USING THE 'OVERALL TOTALS' FIGURE.

THE COMPUTER ESTABLISHES 'RANGE OF PERCENTAGES' FROM THE DATA COMPRISING 'POSITIVE TOTALS'.

CONTROL VALUES IN B6C3F1 MICE-UNTREATED CONTROLS-NEOPLASIA ONLY

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
*** TISSUE NAME--ADRENAL ***				
CORTICAL ADENOMA				
	0	15	1	18
	0	14	1	18
	1	68	3	78
POSITIVE TOTALS--	1	97	5	114
OVERALL TOTALS---	1	310	5	327
OVERALL PERCENT--	0.3		1.5	
RANGE OF PERCENTAGES--	0 --	1	4 --	6
PHEOCHROMOCYTOMA				
	9	68	0	78
POSITIVE TOTALS--	9	68	0	78
OVERALL TOTALS---	9	310	0	327
OVERALL PERCENT--	2.9		0.0	
RANGE OF PERCENTAGES--	13 --	13	0 --	0

CONTROL VALUES IN B6C3F1 MICE-UNTREATED CONTROLS-NEOPLASIA ONLY

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
*** TISSUE NAME--DUODENUM ***				
ADENOMATOUS POLYP (NOS)				
	0	20	1	20
POSITIVE TOTALS--	0	20	1	20
OVERALL TOTALS---	0	69	1	69
OVERALL PERCENT--	0.0		1.4	
RANGE OF PERCENTAGES--	0 -- 0		5 -- 5	
CARCINOMA (NOS)				
	1	49	0	49
POSITIVE TOTALS--	1	49	0	49
OVERALL TOTALS---	1	69	0	69
OVERALL PERCENT--	1.4		0.0	
RANGE OF PERCENTAGES--	2 -- 2		0 -- 0	
*** TISSUE NAME--EYES ***				
MALIGNANT MELANOMA				
	1	20	0	20
POSITIVE TOTALS--	1	20	0	20
OVERALL TOTALS---	1	91	0	100
OVERALL PERCENT--	1.1		0.0	
RANGE OF PERCENTAGES--	5 -- 5		0 -- 0	

CONTROL VALUES IN B6C3F1 MICE-UNTREATED CONTROLS-NEOPLASIA ONLY

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
*** TISSUE NAME--HARDERIAN GLANDS ***				
ADENOMA (NOS)				
	0	50	1	50
	1	70	0	79
POSITIVE TOTALS--	1	120	1	129
OVERALL TOTALS---	1	120	1	129
OVERALL PERCENT--	0.8		0.8	
RANGE OF PERCENTAGES--	0 -- 1		0 -- 2	
CARCINOMA (NOS)				
	1	50	0	50
POSITIVE TOTALS--	1	50	0	50
OVERALL TOTALS---	1	120	0	129
OVERALL PERCENT--	0.8		0.0	
RANGE OF PERCENTAGES--	2 -- 2		0 -- 0	
*** TISSUE NAME--KIDNEY ***				
ADENOCARCINOMA (NOS)				
	1	19	0	19
POSITIVE TOTALS--	1	19	0	19
OVERALL TOTALS---	1	300	0	313
OVERALL PERCENT--	0.3		0.0	
RANGE OF PERCENTAGES--	5 -- 5		0 -- 0	

CONTROL VALUES IN B6C3F1 MICE-UNTREATED CONTROLS-NEOPLASIA ONLY

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
FIBROSARCOMA				
	1	19	0	19
POSITIVE TOTALS--	1	19	0	19
OVERALL TOTALS---	1	300	0	313
OVERALL PERCENT--	0.3		0.0	
RANGE OF PERCENTAGES--	5 --	5	0 --	0
TUBULAR CELL ADENOMA				
	1	70	0	79
POSITIVE TOTALS--	1	70	0	79
OVERALL TOTALS---	1	300	0	313
OVERALL PERCENT--	0.3		0.0	
RANGE OF PERCENTAGES--	1 --	1	0 --	0

*** TISSUE NAME--LIVER ***

HEMANGIOSARCOMA				
	1	19	0	18
	1	20	0	20
	0	70	1	79
POSITIVE TOTALS--	2	109	1	117
OVERALL TOTALS---	2	354	1	369
OVERALL PERCENT--	0.6		0.3	
RANGE OF PERCENTAGES--	0 --	5	0 --	1

CONTROL VALUES IN B6C3F1 MICE-UNTREATED CONTROLS-NEOPLASIA ONLY

FINDING	POSITIVE FINDINGS (MALES)	ANIMALS EXAMINED (MALES)	POSITIVE FINDINGS (FEMALES)	ANIMALS EXAMINED (FEMALES)
HEPATOCELLULAR ADENOMA				
	3	50	1	49
	2	50	1	50
	1	70	0	79
POSITIVE TOTALS--	6	170	2	178
OVERALL TOTALS---	6	354	2	369
OVERALL PERCENT--	1.7		0.5	
RANGE OF PERCENTAGES--	1 --	6	0 --	2
HEPATOCELLULAR CARCINOMA				
	17	50	2	49
	12	50	2	50
	2	19	0	18
	3	17	0	19
	1	20	0	20
	1	20	1	19
	3	19	1	19
	2	20	2	20
	2	20	0	20
	15	70	0	79
POSITIVE TOTALS--	57	305	8	313
OVERALL TOTALS---	57	354	8	369
OVERALL PERCENT--	16.1		2.2	
RANGE OF PERCENTAGES--	5 --	34	0 --	10

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE VIENNA, VIRGINIA 22180 U S A

REPRESENTATIVE HISTORICAL CONTROL DATA

PART 1: RODENT SURVIVAL DATA

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE VIENNA VIRGINIA 22180 U S A

REPRESENTATIVE HISTORICAL CONTROL DATA - CONTINUED

Appendix 17: Adjusted Survival Data - CD®-1 Control Mice Treated with Distilled Water Administered by Gavage - Individually Housed

Appendix 18: Adjusted Survival Data - CD®-1 Control Mice Treated with 0.5% Tragacanth in Distilled Water Administered by Gavage - Individually Housed

Appendix 19: Adjusted Survival Data - CD®-1 Control Mice Treated with Acetone Administered in the Diet - Individually Housed

Appendix 20: Adjusted Survival Data - Untreated B6C3F1 Mice - Group Housed

Appendix 21: Adjusted Survival Data - B6C3F1 Control Mice Treated with Glacial Acetic Acid in the Drinking Water - Individually Housed

Appendix 22: Adjusted Survival Data - B6C3F1 Control Mice Receiving Deionized Drinking Water - Individually Housed Bioclean®

PART 2: NEOPLASIA IN UNTREATED SPRAGUE-DAWLEY RATS

PART 3: NEOPLASIA IN UNTREATED SPRAGUE-DAWLEY F1 RATS

PART 4: NEOPLASIA IN UNTREATED SPRAGUE-DAWLEY CONTROL RATS TREATED WITH 95% ETHANOL IN THE DIET

PART 5: NEOPLASIA IN SPRAGUE-DAWLEY CONTROL RATS TREATED WITH GLACIAL ACETIC ACID IN THE DRINKING WATER

PART 6: NEOPLASIA IN UNTREATED FISCHER 344 RATS

PART 7: NEOPLASIA IN UNTREATED FISCHER 344 F1 RATS

PART 8: NEOPLASIA IN FISCHER 344 CONTROL RATS RECEIVING DEIONIZED DRINKING WATER

PART 9: NEOPLASIA IN FISCHER 344 CONTROL RATS TREATED WITH 0.5% TRAGACANTH IN DISTILLED WATER ADMINISTERED BY GAVAGE

PART 10: NEOPLASIA IN FISCHER 344 CONTROL RATS TREATED WITH DISTILLED WATER ADMINISTERED BY GAVAGE

PART 11: NEOPLASIA IN UNTREATED LONG EVANS HOODED F1 RATS

PART 12: NEOPLASIA IN UNTREATED B6C3F1 MICE

PART 13: NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CORN OIL IN THE DIET

PART 14: NEOPLASIA IN B6C3F1 CONTROL MICE WITH CORN OIL ADMINISTERED BY GAVAGE

PART 15: NEOPLASIA IN B6C3F1 CONTROL MICE TREATED WITH CARBOXYMETHYLCELLULOSE ADMINISTERED BY GAVAGE

PART 16: NEOPLASIA IN UNTREATED CD®-1 MICE

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE VIENNA VIRGINIA 22180 U S A

REPRESENTATIVE HISTORICAL CONTROL DATA

PART 1: RODENT SURVIVAL DATA

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE VIENNA VIRGINIA 22180 U S A

REPRESENTATIVE HISTORICAL CONTROL DATA - CONTINUED

PART 17: NEOPLASIA IN UNTREATED CD®-1 F1 MICE
PART 18: NEOPLASIA IN CD®-1 CONTROL MICE TREATED WITH DISTILLED WATER ADMINSTERED BY GAVAGE
PART 19: NEOPLASIA IN CD®-1 CONTROL MICE TREATED WITH 0.5% TRAGACANTH IN DISTILLED WATER ADMINISTERED BY GAVAGE
PART 20: HEMATOLOGY REFERENCE RANGES
PART 21: CLINICAL CHEMISTRY REFERENCE RANGES
PART 22: BASIC STATISTICS FOR BODY WEIGHT DATA

Table 1: Basic Statistics for Historical Body Weight Data (Grams) - Fischer 344 Rats - Control Animals
Table 2: Basic Statistics for Historical Body Weight Data (Grams) - Fischer 344 Control Animals by Treatment and Housing

NOTE: Historical control data generated in-house at Hazleton Laboratories America, Inc.

Updated 3/5/84

13544

046410

Chemical:	**Tetramethrin**
PC Code:	**069003**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/15/86**
File ID:	**00000000**
Accession Number:	**412-03-0116**

HED Records Reference Center
06/30/2003