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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin - Results of Histological Analysis of
Eye Lesions in Rat Reproduction Study (TT#82-9010)
NRID NO. 00164151

Caswell No.: 63AB
Dynamac No.: 326
EPA No.: 3-26

FROM: William G. Dykstra *William Dykstra*
Toxicology Branch
Hazard Evaluation Division (TS-769C) *11/3/87*

TO: George T. LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Edwin R. Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C) *11/5/87*

In the review of April 23, 1987, Avermectin on Citrus (PP#7H5518/7G3468), the two-generation rat reproduction study with avermectin displayed a possible compound-related increase in retinal anomalies in F_{2b} weanlings at 0.40 mg/kg/day (HDT). The distribution of the findings in the reviewed study is shown below:

Dose (mg/kg/day)	<u>F_{2b} Weanlings (Merck)</u>							
	0		.05		.12		.40	
	M	F	M	F	M	F	M	F
Number Examined	57	51	26	34	88	86	63	66
Retinal Anomaly	3	2	0	1	5	2	10	18

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As reported by the registrant (Merck), "the anomalies were in the form of single or multiple retinal folds of many layers that included pigment epithelium in the center. Some appeared as intra-retinal rosettes and in others the connection with the pigment layer was seen in the section."

Toxicology Branch (TB) requested that the slides of the eyes for all test animals be submitted for further evaluation. The Experimental Pathology Laboratories, Inc. (EPL) pathology report of the evaluation has been received (Dynamac Corporation Study Number TT#82-9010).

The following information has been obtained from the EPL report.

"Microscopic examinations were performed on hematoxylin and eosin stained sections of right and left eyes from 75² rats [CAL:COBS(SD)BR] used in a multigeneration gavage study of Abamectin. The eyes were evaluated from a total of 39 F1b weanlings, 249 F1b adults, and 470 F2b weanlings. The individual groups were arbitrarily assigned to groups one through twelve to facilitate tabulation of the results. The group assignment, generation, treatment, and number of animals are summarized in the following table:

Group*	Generation	Treatment (mg/kg/day)	Number of Rats		Total
			Males	Females	
1	F1b Weanlings	0	5	5	10
2	F1b Weanlings	0.05	5	5	10
3	F1b Weanlings	0.12	5	5	10
4	F1b Weanlings	0.40	4	5	9
5	F1b Adults	0	30	32	62
6	F1b Adults	0.05	31	31	62**
7	F1b Adults	0.12	31	32	63
8	F1b Adults	0.40	31	31	62
9	F2b Weanlings	0	57	51	108
10	F2b Weanlings	0.05	26	34	60
11	F2b Weanlings	0.12	88	85	173***
12	F2b Weanlings	0.40	63	66	129

*Number assigned for computerization purposes.

**Number of slides received on animals 119498 and 119499.

***Number of slides received on animal 122293."

The microscopic changes in the retina are presented below as stated in the EPL report:

MICROSCOPIC CHANGES IN THE RETINA

	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	M	F	M	F	M	F	M	F	M	F	M	F
No. Examined	(5)	(5)	(5)	(5)	(5)	(5)	(4)	(5)	(30)	(32)	(31)	(31)
Retinal Folds, Unilateral	-	-	-	-	-	-	2	-	1	1	1	-
Retinal Folds, Bilateral	-	-	-	-	-	-	-	1	-	-	-	-
Retinal Rosettes, Unilateral	-	-	-	-	1	-	-	-	-	-	-	-
Retinal Rosettes, Bilateral	-	-	-	-	-	-	2	-	-	-	-	-
Dysplasia, Optic Disc, Unilateral	-	-	-	-	-	-	-	-	-	-	-	1
Dysplasia, Optic Disc, Bilateral	-	-	-	-	-	-	-	-	-	-	-	-
Retinal Fold(s), Ora Serrata, Unilateral	-	1	1	1	1	1	-	1	-	-	-	-
Retinal Fold(s), Ora Serrata, Bilateral	-	-	-	-	-	-	-	-	-	-	-	-

	Group 7		Group 8		Group 9		Group 10		Group 11		Group 12	
	M	F	M	F	M	F	M	F	M	F	M	F
No. Examined	(31)	(32)	(31)	(31)	(57)	(51)	(26)	(34)	(88)	(85)	(63)	(56)
Retinal Folds, Unilateral	1	-	6	-	10	7	2	5	12	13	10	12
Retinal Folds, Bilateral	-	-	1	-	1	5	1	-	2	1	4	4
Retinal Rosettes, Unilateral	-	-	2	-	2	4	-	2	5	-	6	12
Retinal Rosettes, Bilateral	-	-	-	-	1	-	-	-	-	-	-	1
Dysplasia, Optic Disc, Unilateral	-	-	-	-	10	5	2	3	14	19	5	4
Dysplasia, Optic Disc, Bilateral	-	-	-	-	2	-	-	3	1	2	-	1
Retinal Fold(s), Ora Serrata, Unilateral	-	-	1	-	4	1	1	4	13	6	5	3
Retinal Fold(s), Ora Serrata, Bilateral	-	-	-	-	-	1	-	-	1	-	-	2

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Statistical analyses of the data did not demonstrate any significant, dose-related positive effects. Statistical analysis was conducted, by sex, for groups 9, 10, 11, and 12 (F_{2b} weanlings). The retinal lesions analyzed were: 1) retinal folds, unilateral; 2) retinal rosettes, unilateral; 3) dysplasia, optic disc, unilateral; and 4) retinal folds, ora serrata, unilateral.

No adjustment was made for a possible "litter effect" in the F_{2b} weanling data. Litter designation for the examined weanlings was not provided by the registrant. The retinal lesions in the EPL report, which correspond to the registrant's "retinal anomaly," are retinal rosettes, unilateral. These lesions occurred in the following distribution:

Dose (mg/kg/day)	<u>F_{2b} Weanlings (EPL Report)</u>							
	0		.05		.12		.40	
	M	F	M	F	M	F	M	F
Number Examined	57	51	26	34	88	85	63	66
Retinal Rosettes, Unilateral	2	4	0	2	5	0	6	12

In light of the statistical analyses and the fact that the grades of the lesions were comparable between control and treated groups, these results suggest that there was no compound-related retinal lesion in the F_{2b} weanlings.

Additionally, the lack of bilateral occurrence of retinal rosettes also leads to the conclusion that this finding is an incidental change.

The pathologist, Dr. Larry J. Ackerman, who evaluated the slides for EPL states that "However, the higher incidences of retinal rosettes in the animals receiving 0.40 mg/kg/day of Abamectin suggest a treatment-related effect at this dosage level. This effect was not present in the low dose (0.05 mg/kg/day) and equivocal in the mid dose (0.12 mg/kg/day). The dosage of 0.05 mg/kg/day could be considered the no-observed-effect level (NOEL). In most of the weanling rats with the minimal to slight retinal changes, there should only be a focal visual impairment in the eye (usually unilateral) as an adult. A few rats in which the changes were more pronounced may have had more visual impairment if allowed to fully develop into adults."

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Conclusion and Recommendations

TB concludes, based on the available data, that the NOEL for retinal rosettes, unilateral, is 0.2 mg/kg/day for the F_{2b} weanlings of the two-generation rat reproduction study with Avermectin. The LEL is 0.40 mg/kg/day and the effect is an increased incidence of retinal rosettes, unilateral, in the F_{2b} weanlings.

Classification

The study was previously classified as Supplementary. Based on the TB evaluation of the slides of the eyes, the study is therefore upgraded to Core-Minimum which supports the registration.

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