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

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JUL 11 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Tetramethrin; EPA Reg. No. 10308-1; Addendum To: Cancer Risk Assessment for Neo-pynamin (Dated September 8, 1982 and Signed July 21, 1984)

Caswell No. 844
Record No. 187795
Project No. 7-0361
Accession No. 248341

TO: Paul Schroeder
Product Manager 17
Registration Division (TS-767)

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

FROM: William Dykstra
Toxicology Branch
Hazard Evaluation Division (TS-769)

Requested Action:

Review addendum to Dr. Calborg risk assessment for neo-pynamin.

Conclusion and Recommendation:

1. Attached is the August 12, 1985 risk assessment from B. Fisher of TB based on the summary data only for the Sprague-Dawley (1974 and 1981) and Long-Evans (1981) rat studies. Due to the preliminary findings of possible oncogenicity in these studies, the oncogenic potential of tetramethrin will be evaluated by the TB Peer Review Committee. TB presently has the necessary raw data from the three rat studies and will perform life-table analyses and statistical analyses for these studies for presentation to the Peer Review Committee.

If necessary, the Q_1^* (determined in the August 12, 1985 memo from TB) will be re-evaluated following the TB Peer Review Committee conclusions. The newly submitted addendum will be addressed at that time.

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

AUG 12 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

SUBJECT: Preliminary Risk Assessment of Tetramethrin - Based on Sprague-Dawley (1974 and 1981) and Long Evans Rat (1981) Studies
Registration No. 10308-1 Caswell No. 844

FROM: Bernice Fisher, Statistician
Toxicology Branch/HED (TS-769)
Bernice Fisher 8/12/85

TO: John Doherty, Ph.D., Toxicologist
Toxicology Branch/HED (TS-769)

THRU: Bertram Litt, Leader, Statistics Team
Mission Support Staff
Toxicology Branch/HED (TS-769)
Aug 12, 1985

and

Reto Engler, Ph.D.
Chief, Mission Support Staff
Toxicology Branch/HED (TS-769)

Summary

This Risk Assessment responds to the one that was prepared by Dr. F. W. Carlborg for the Registrant.

A weight of evidence determination for Tetramethrin has not been done nor has it been examined by the Toxicology Branch Review Committee. Therefore, the dose exposure analysis of the rat studies alone should not be used for a risk characterization and regulatory actions (e.g. registration, special review, etc.).

The following evaluation of statistics derived from three studies indicates that Tetramethrin is associated with an increase of testicular interstitial adenomas in rats of the Sprague-Dawley and Long Evans strains.

The potency factor is Q_1^* of 1.2×10^{-2} for Tetramethrin, is expressed in $(mg/kg\ body\ weight/day)^{-1}$ and is based upon the 1974 Sprague-Dawley rat study. This factor may be revised if subsequent mouse data demonstrates higher risks.

Background

Hazleton Labs conducted three 2-year chronic feeding studies of rats for the Sumitomo Chemical Co.

In the first one (1974), Tetramethrin (Neopynamin) was fed to Sprague-Dawley rats (120 males and 120 females) one week prior to breeding and continued for 104 weeks following weaning. The dose levels were 1000, 3000 and 5000 parts per million (ppm). The concurrent controls consisted of 50 males and 50 females.

Since the only single positive effect reported in this study (1974) was the increasing incidence of testicular interstitial cell adenomas, the 1981 studies were created similar in design to the earlier one in order to reassess this finding.

Study Description

In the 1974 study, F_1 generation of male pups were selected after weaning and were placed on the same diet as their parents: 60 controls and 50 per Tetramethrin doses of 200, 3000 and 5000 parts per million.

While in the 1981 study, after weaning male F_1 offspring of each strain/group were selected at random with no more than three pups per litter as the samples to be pathologically examined and evaluated. The dose levels of Tetramethrin in these two studies were 0, 200, 1000 and 5000 parts per million.

The three studies generated the following data on number of adenomas, survival, food consumption and weight changes during the 104 weeks of observations.

Table 1. Tetramethrin Chronic Study - Number of Rats - Males, F_1 (104 weeks)

Group	Strain	Date of Study	Dose (ppm) 0	200	1000	3000	5000
I	Sprague-Dawley	1974	50	40	--	40	40
II	Sprague-Dawley	1981	50	50	50	--	50
III	Long Evans	1981	50	50	50	--	50

Table 2. Tetrametrin Chronic Study - Testicular Interstitial Adenomas as a Proportion of Survivors in Rats - Males, F_1 (80 weeks)

Group	Strain	Date of Study	Dose (ppm) 0	200	1000	3000	5000
I	Sprague-Dawley	1974	2/44	--	3/30	9/36	14/37
II	Sprague-Dawley	1981	7/41	7/45	3/41	--	16/40
III	Long Evans	1981	4/43	3/44	4/43	--	22/47

Table 3. Tetrametrin Chronic Study - Testicular Interstitial Adenomas as a Proportion of Survivors in Rats - Males, F_1 (104 weeks)

Group	Strain	Date of Study	Dose (ppm) 0	200	1000	3000	5000
I	Sprague-Dawley	1974	1/33	--	1/17	8/29	9/22
II	Sprague-Dawley	1981	7/30	3/26	2/26	--	12/30
III	Long Evans	1981	4/37	2/37	3/34	--	19/34

Table 4. Tetramethrin Chronic Study - Survival of Rats - Males, F (104 weeks)

Group	Strain	Date of Study	Dose (ppm) 0	200	1000	3000	5000
I	Sprague-Dawley	1974	33/50	17/40	--	29/40	22/40
II	Sprague-Dawley	1981	30/50	26/50	26/50	--	30/50
III	Long Evans	1981	37/50	37/50	34/50	--	34/50

Table 5. Tetramethrin Chronic Study - Food Consumption, g in Rats - Males, F_1 (104 weeks)

Group I - Sprague-Dawley, 1974

	Dose (ppm)			
Week	0	1000	3000	5000
0	0	0	0	0
26	189	175	174	170
52	188	167	176	168
80	177	173	171	162
104	177	165	162	158

Group II - Sprague-Dawley, 1981

	Dose (ppm)			
Week	0	200	1000	5000
0	0	0	0	0
26	160	166	162	151
52	152	153	147	145
80	168	156	153	155
104	133	132	128	131

Group III - Long Evans, 1981

	Dose (ppm)			
Week	0	200	1000	5000
0	0	0	0	0
26	154	157	157	151
52	144	145	146	146
80	157	157	153	149
104	128	127	129	127

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Table 6. Tetramethrin Chronic Study - Weight, g in Rats - Males, F_1 (104 weeks)

Group I - Sprague-Dawley, 1974

	Dose (ppm)			
Week	0	1000	3000	5000
0	148	131	118	98
26	594	573	530	492
52	664	636	567	545
80	668	630	599	531
104	593	564	531	512

Group II - Sprague-Dawley, 1981

	Dose (ppm)			
Week	0	200	1000	5000
0	268	241	251	229
26	607	608	585	531
52	687	682	650	606
80	682	666	672	611
104	645	661	662	558

Group III - Long Evans, 1981

	Dose (ppm)			
Week	0	200	1000	5000
0	245	236	225	208
26	554	549	541	490
52	632	631	610	566
80	660	655	628	556
104	608	618	608	538

Qualitative Analysis

The 104 weeks survival pattern in all three studies exhibited no dose-related trend (see Table 4).

The incidence of testicular adenomas in F_1 rats, at 80 weeks, in each of the three studies was found to have a strong linear trend with increasing doses of Tetramethrin ($p < .001$). See following analysis based upon the Cochran-Armitage Trend test:

		X^2 Linear Trend	P value
Sprague-Dawley	1974	16.87	4.0×10^{-5}
Sprague-Dawley	1981	11.56	6.8×10^{-4}
Long Evans,	1981	32.63	1.1×10^{-8}

The increments of the same tumors in 104 weeks in each of the three studies were found to have similar strong linear trends with increasing doses of Tetramethrin. Statistical analyses were not prepared because it just reiterated the same conclusion that was shown in the 80th week of the study.

Food consumption and weight gains were both adversely affected on increasing doses of Tetramethrin as compared with controls in each of the three studies.

Quantitative Risk Assessment

Dr. Carlborg combined the data on testicular interstitial adenomas from the above three studies (1974 and 1981) under the following assumptions:

(1) Rats were exposed to lifetime ingestion;

(2) Estimate of human exposure would be according to anticipated use; and

(3) Tetramethrin is a human carcinogen.

The decision to combine all three studies at first glance appears to be justifiable in terms of having a larger number of animals for input in the risk assessment procedure. However, when examining and comparing the studies, some serious drawbacks become evident. They are as follows:

(1) There is a significant difference in the proportion of tumors that occur in the three control groups (see Table 3). In comparing Sprague-Dawley controls, 1974 and 1981, $p < .02$ (Fisher's Exact Test).

(2) The 1974 study data indicate that 3000 ppm is the lowest dose demonstrating a statistically significant ($p < .01$, Fisher's Exact Test) increase in tumor rate compared with the study's control. Therefore, additional studies (i.e., 1981) should have been designed to explore the nature of the dose response between 3000 and 1000 ppm (i.e., between the LOEL and NOEL) as suggested by the 1974 study.

(3) Data at dose 3000 ppm are only available for one of the three groups, namely the 1974 Sprague-Dawley strain study and no doses between 1000 and 3000 have been used for evaluation.

(4) Two of the three study groups are the Sprague-Dawley strains in 1974 and 1981 and one is Long Evans strain in 1981.

Due to the above considerations, it was decided to statistically evaluate (Krewski Program and Global 83) and to calculate an upper bound risk (Q_1^*-Global 83) for each of the three studies as well as the combined groups.

The doses of Tetramethrin were administered as ppm mixed into the diet. To perform the low-dose extrapolations, the doses were corrected first to mg/kg/day in rats and then to mg/kg/day in humans as follows:

One mg/kg rat body wt/day = 20 ppm (Lehman 1959 Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, Assoc. of Food Drug Officials of the U.S.)

$$\frac{60{,}000 \text{ g Human body wt}}{500 \text{ g Rat body wt}} \; 1/3 \sim 5$$

$$\text{ppm dose in rats} \times \frac{1}{20} \times \frac{1}{5} = \text{mg Tetramethrin/kg body wt/day}$$

The results of fitting the data in each of the three studies to selected models reinforced our decision of not combining the data from the three studies (see table 7). It was evident that the three studies should not combined because each of them seem to belong to a different distribution. The best fitted data comes from the Sprague-Dawley 1974 study and the worse from the Sprague-Dawley 1981 study. The data from each of the studies were also used in the Linearized Multistage Procedure (Global 83) in order to estimate an upper bound risk, Q_1^* (95% Confidence Limit) for each study.

The Q_1^* potency estimates in Table 8 show about 1/2 order of magnitude difference among the studies. However, if the data were to be combined, the preferred method would be to calculate a

Geometric Mean (see Table 8). This value could be used as an alternative to the one suggested in the summary section of this report. However, as there is a statistically significant dose response (Cochran-Armitage Test) at 3000 ppm in the 1974 study compared to the 5000 in the other two studies, extrapolation for the calculation of Q_1^* obviously should be based on the 1974 study alone.

Table 7. Tetramethrin - Comparisons of Fit of Data Models - Independent Background in Probit, Logit and Weibul Multistage Curves

Strain of Rat and Date of Study		Model			
		Probit	Logit	Weibul	Multistage
All (1974 and 1981)	X^2	0.346	0.346	0.346	0.447
	p	0.56	0.56	0.56	0.11
Sprague-Dawley (1974)	X^2	0.005	0.001	0.010	0.029
	p	0.94	0.98	0.92	$\leq$ 0.50
Sprague-Dawley (1981)	X^2	1.966	1.966	1.966	2.058
	p	0.16	0.16	0.16	$\sim$ 0.07
Long Evans (1981)	X^2	0.182	0.184	0.185	0.187
	p	0.67	0.67	0.67	< 0.45

Source: D. Krewski and Global 83 Program

Table 8. Tetramethrin - Q_1^*s (95% Upper Bound Risk) and its Geometric Mean

Rat Strain	Q_1^*
All	5.5×10^{-3}
Sprague-Dawley (1974)	1.2×10^{-2}
Sprague-Dawley (1981)	6.9×10^{-3}
Long Evans (1981)	1.2×10^{-2}

Geometric Mean

$$Q_1^* = ((1.2 \times 10^{-2})(6.9 \times 10^{-3})(1.2 \times 10^{-2}))^{1/3}$$

$$= 1.0 \times 10^{-2}$$

Source: Global 83 - Crump, K.S.

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ADDENDUM TO: CANCER RISK ASSESSMENT FOR NDO-PYNAMIN (DATED SEPTEMBER 8, 1982)

By Frank W. Carlborg

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July 21, 1984
Date

ADDENDUM

This report is an addendum to a previous report of September 8, 1982, which was titled "Cancer Risk Assessment for Neo-Pynamin". Based on the results from three laboratory experiment with rats and on the estimated human exposure, a cancer risk assessment was given. The human exposures have now been modified. The report in hand gives the corresponding modified cancer risk assessment.

Tables 1-4 of the previous report refer to the results from the laboratory experiments, and they remain unchanged. Table 5 has been modified, and it is given here.

The first column of Table 5 gives the four categories of persons exposed to Neo-Pynamin. The second column refers to an outline in a Table in the Addendum to the statement of Dr. Clive A. Edwards (CAE), who provided the modified human exposures. The third column gives the corresponding human exposures, also taken from the Table of Dr. Edwards. The last four columns give the estimated lifetime cancer risks for the two models and their upper 95% confidence limits. The maximum risk in the entire table is 5.7×10^{-3}, or 5.7 in 100 million.

The summary statement in the original report of September 8, 1982 still applies. Mainly, the estimated human cancer risk from an exposure to Neo-Pynamin is essentially zero regardless of how one performs the risk assessment.

TABLE 5 (modified): Human risk estimates (best estimate and upper 95% confidence limit) according to the Weibull and low-dose linear models for all categories of human exposure.

category	CAE table number	equivalent lifetime dose in ppm	Weibull		low-dose linear	
			best est.	95% CL	best est.	95% CL
aerosol	1a	0.000051	<1.0 -10	<1.0 -10	<1.0 -10	2.9 -9
user	1b	0.000034	<1.0 -10	<1.0 -10	<1.0 -10	2.0 -9
	1c	0.000979	<1.0 -10	6.9 -10	8.2 -10	5.7 -8
inhabitant	2	0.00000092	<1.0 -10	<1.0 -10	<1.0 -10	<1.0 -10
industrial applicator	3	0.0006921	<1.0 -10	4.4 -10	5.8 -10	4.0 -8
spray applicator	4	0.000913	<1.0 -10	6.3 -10	7.7 -10	5.3 -8

where, for example, 5.7 -8 means 5.7×10^{-8} or 5.7 in 100 million.

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Chemical:	**Tetramethrin**
PC Code:	**069003**
HED File Code	**21200 CARC**
Memo Date:	**07/11/88**
File ID:	**TX007655**
Accession Number:	**412-03-0116**

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