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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

Subject: Permethrin - Quantitative Risk Assessment,
Two Year Chronic/Oncogenicity Mouse(Females)
Study

caswell no. 652BB

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Summary:

The unit risk, Q_1^*(mg/kg/day)$^{-1}$ of permethrin is 1.84×10^{-2} [c_q] in human equivalents. The estimate, Q_1^* was based upon the female mouse lung (adenoma and/or carcinoma) tumors which were the most sensitive to the dose increments of permethrin.

Survival in female mice was not significantly dose related. See the inclosed memorandum on Permethrin - Qualitative Risk Assessment, Two Year Chronic/Onco Mouse Study, B.Fisher, 9/88 for details on all the statistically significant findings on the aforementioned tumors in female mice that were used to estimate the Q_1^*.

cc R. Engler

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Background

In December 1988, the Peer Review Committee recomended that a quantitative risk assessment of permethrin be prepared from CD-1 mouse data in a 2-year feeding study by Bio/Dynamics Inc. for FMC Corporation, October, 1979.

The qualitative risk assessment (See Permethrin - Qualitative Risk Assessment, Two Year Chronic/Onco Mouse Study, B. Fisher, 9/88) indicated that female mice did not have any significant differential survival with dose increments of permethrin. Male mice had a significantly increasing trend in mortality, mainly due to a significant difference in mortality in the highest dose group as compared with controls.

The following text and tables contain the statistical findings from the memorandom on the permethrin qualitative risk assessment.

Significant increasing tumorgenicity occurred in the lungs and liver of the female mice with increasing doses of permethrin.

Female mice had significant trends in lung adenomas, lung carcinomas, and in lung adenomas and/or carcinomas. In addition, all of the 3 tumor types had significant differences in the pairwise comparison of control and the highest (5000 ppm.) dose group. Also lung adenomas and lung adenomas and/or carcinomas had significant differences in the pairwise comparisons of controls with both the low (20 ppm.) and the mid (2500 ppm.) dose groups. See Table 4. for details.

In female mice, liver adenomas and also liver adenomas and/or carcinomas had significantly increasing trends with incremental doses of permethrin. The pairwise comparisons with controls resulted in significant differences in the mid (2500 ppm.) and also the high (5000 ppm.) dose group for both liver adenomas and liver adenomas and/or carcinomas. Liver carcinomas did not increase significantly. See Table 5. for details.

For male mice, because of significant survival differentials among the dose levels of permethrin, tumor data was statistically evaluated for trends and the pairwise comparisons by means of Peto's Prevalence test.

As in female mice, males also had liver and lung tumors. But in males, lung tumors did not significantly increase with dose increments of permethrin. See Table 6. for details.

In male mice liver adenoma tumor rates had significantly increasing trends. The pairwise comparison of controls and each of the 3 (20, 500, 2000 ppm.) dose groups had significant differences in liver adenoma tumor rates. For the combined liver (adenomas and/or carcinomas) tumor rates, there were significant differences between controls and and the mid (500 ppm.) and also the high (2000 ppm.) dose group. In male mice just as in females, liver carcinomas were not significantly elevated with incremental doses of permethrin. However in males, the control group had a 24 % tumor rate of liver carcinomas. See Table 7. for details.

Table 4. Permethrin - Mouse Study, Female Lung Tumor Rates† and Cochran-Armitage Trend Test and Fisher Exact Test Results

Tumor	Dose (ppm) 0	20	2500	5000
Adenoma	9/71	17/68	24/68	29/69
(%)	(13)	(25)	(35)[a]	(42)
p =	0.0002**	0.0495*	0.0015**	0.0001**
Carcinoma	6/66	7/62	11/59	15/62
(%)	(9)	(11)[b]	(19)	(24)
p =	0.0047**	0.4519	0.0977	0.0187*
Both	15/71	24/68	35/68	44/69
(%)	(21)	(35)	(52)	(64)
p =	0.0000**	0.0473*	0.0002**	0.0000**

†Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.

[a]First adenoma at week 39.

[b]First carcinoma at week 62.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.

*p < .05.

**p < .01.

Table 5. Permethrin, Mouse Study - Female Liver Tumor Rates[†] and Cochran-Armitage Trend Test and Fisher Exact Test Results

Tumor	Dose (ppm) 0	20	2500	5000
Adenoma	2/66	4/62	22/63	28/65
(%)	(3)	(6)	(35)[a]	(43)
p =	0.0000**	0.2994	0.0000**	0.0000**
Carcinoma	4/49	3/55	3/49	2/51
(%)	(8)	(5)	(6)	(4)
p =	0.2534	0.4312	0.4938	0.3082
Both	6/66	7/62	25/63	30/65
(%)	(9)	(11)	(40)	(46)
p =	0.0000**	0.4519	0.0000**	0.0000**

[†]Number of tumor-bearing animals that died/Number of animals at risk, excluding those that died before observation of the first tumor.
[a]First adenoma at week 54.
[b]First carcinoma at week 81.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Table 6. Permethrin, Mouse Study - Male Lung Tumor Rates[†] and Peto Prevalence Test Results

Tumor	Dose (ppm) 0	20	500	2000
Adenoma	16/73	15/71	15/68	17/69
(%)	(22)	(21)	(22)[a]	(25)
p =	0.1175	0.4651	0.4823	0.1707
Carcinoma	7/49	5/52	13/54	4/30
(%)	(14)	(10)[b]	(24)	(13)
p =	0.3989	0.2217	0.1276	0.1722
Both	23/73	20/71	28/68	21/69
(%)	(32)	(28)	(41)	(30)
p =	0.1329	0.3585	0.1535	0.1722

[†]Number of tumor-bearing animals that died/Number of animals at risk, excluding those that died before observation of the first tumor.
[a]First adenoma at week 25.
[b]First carcinoma at week 81.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Table 7. Permethrin, Mouse Study - Male Liver Tumor Rates and Peto Prevalence Test Results

Tumor	Dose (ppm) 0	20	500	2000
Adenoma	6/66	17/63	15/63	17/57
(%)	(9)	(27)	(24)	(30)[a]
p =	0.0034**	0.0058**	0.0150*	0.0003**
Carcinoma	16/68	12/64	19/64	8/60
(%)	(24)	(19)	(30)[b]	(13)
p =	0.1797	0.3481	0.1381	0.1819
Both	22/68	29/64	36/64	25/60
(%)	(32)	(45)	(56)	(42)
p =	0.0973	0.0618	0.0083**	0.0215*

[†]Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.
[a]First adenoma at week 56.
[b]First carcinoma at week 47.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.
*p < .05.
**p < .01.

Dose-Responce

The Peer Review Committee suggested that since in female mice both lung and liver tumorgenicity were significant occurrences with dose increments of permethrin, the calculation of the unit risk should be made by the use of each of the significant tumor types.

It was also suggested by one member of the committee to combine lung and liver tumors since the EPA Guidelines advises the following: "When two or more significantly elevated tumor sites or types are observed in the same study extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation" (F.R. 51: 33997, 9/24/86).

As recommended by EPA Cancer Risk Assessment Guidelines, the Multi-Stage Global86 Model was used to estimate the the unit risk, Q_1^*, since female mice had no survival differences with incremental doses of permethrin. The unit risk, based upon the female mouse data in ppm. was converted to mg/kg/day by the use of Lehman's Tables and then to human equivalents by the use of the interspecies surface area adjustment+ as suggested by EPA Cancer Guidelines (F.R. 51: 33993-34014, 9/24/86) and under the assumption that the adult weight of the mouse is .025 kg. and of humans is 60 kg.

In following the recommendations of EPA Cancer Guidelines to indicate the contribution of the benign tumors to total risk- The quantitative models are first fit to the malignant tumors and then fit to the combined tumors. The difference in the unit risk between combined and the malignant is the result of considering the benign tumor to progress to malignant.

It is to be noted that Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the the upper (95%) bound on risk and that (as stated in the EPA Risk Assessment Guidelines) "the true value of the risk is unknown, and may be as low as zero."

+ $\left(\frac{\text{human wt.-grams}}{\text{animal wt.-grams}}\right)^{1/3}$

The resultant estimates of $Q_1^*(mg/kg/day)^{-1}$ are as follows:

Tumors (adenomas &/or carcinomas)	female mouse	human equivalents	Tumors (carcinomas)	female mouse	human equivalents
Lung	1.37×10^{-3}	1.84×10^{-2}	Lung	4.27×10^{-4}	5.71×10^{-3}
Liver	1.11×10^{-3}	1.48×10^{-2}	Liver	7.25×10^{-5}	9.7×10^{-4}
Lung & Liver	1.86×10^{-3}	2.49×10^{-2}	Lung & Liver	4.40×10^{-4}	5.90×10^{-3}

In the estimates of unit risk from both the lung and liver tumor rates, the significant adenoma increments were responsible for less than one order magnitude and two orders magnitude, repectively, in the estimate of total risk. Therefore, the unit risk, Q_1^* was based upon the lung tumor(adenoma and/or carcinoma) because the contribution to the total risk of malignant tumors was greater than in the liver.

References

Howe, R.B., Crump, K.S. and Van Landingham, C. (1986)
A Computer Program to Extrapolate Quantal Animal
Toxicity Data to Low Doses (unpublished report), 25 pgs.