5-26-81
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MEMORANDUM

Date:- May the 26th, 1981.

To:- Christine Chaisson, Toxicology Branch

From:- M. Adrian Gross, HED

Subject:- Permethrin - carcinogenicity - Biodynamics rat study.

The following is pursuant to your request that I help out in the review and evaluation process of the FMC rat study carried out with permethrin at Biodynamics Inc.

The assessment of the results yielded by this study was carried out exclusively by Mr. Burin; my own contribution to this work of his was to offer him advice and suggestions whenever he requested these. It is my overall impression that he has carried out a very thorough analysis where all relevant issues were addressed in a highly competent manner. The product of his work can well serve as a model in the Toxicology Branch on how carcinogenicity studies ought to be approached in the course of review and evaluation.

From his analysis it appears that the most critical finding was the incidence of primary lung tumors amongst male rats. It is noteworthy that the lung was one of the two sites of principal interest as far as tumor induction was concerned in the second mouse study with permethrin which was also conducted at Biodynamics. For a review of those findings, see my letter to Pat Critchlow of last January the 19th as well as my presentation before the SAP of March 10th, this year.

Mr. Burin's findings can be supplemented by the following comments of a statistical nature:-

The primary pulmonary tumors noted in the male rats in the study under reference were without exception found only in the animals having survived the full course of the observation period. In this sense, all such tumors can be considered as being "incidental tumors" as distinct from tumors about which it can be said that they may have caused the demise of their hosts; also, because of this feature, no corrections or adjustments (such as a life-table procedure) for the population at risk at any time are necessary. Rather the number of animals at risk is confined precisely to the number of "terminal survivors".

The following is the distribution of male animals positive for primary lung tumors by reference to the animals at risk in the various experimental groups:-

ppm	Proportion Positive	99% confidence limits	
		Lower	Upper
0	1/45 = 2.22%	0.01%	
20	3/37 = 8.11%		26.63%
100	8/39 = 20.51%		41.43%
500	6/39 = 15.38%		35.40%

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Simple inspection of these data reveals a lack of a monotonically increasing function throughout the range of exposure levels tried in this study; the only aberration to this rule is provided by the response noted at the top exposure level which is probably due to competing toxicity having inhibited the full expression of the neoplastic potential at this very high level - 500 ppm.

Even so, however, most of the differences noted in the response at various levels or combination of levels are statistically significant to a remarkable degree:-

Contrast Examined	Relative Risk	Probability (hypergeometric distribution)
0 ppm vs. 100 ppm	11.35	0.008,096
0 ppm vs. 500 ppm	8.00	0.035,811
0 ppm vs. 100 and 500 ppm	9.62	0.007, 193
0 ppm vs. 20, 100, and 500 ppm	7.13	0.016, 107
0 and 20 ppm vs. 100 and 500 ppm	4.27	0.008,198

A trend analysis for proportions restricted to the response noted at the control, low and middle levels of exposure reveals the following:-

estimate of the slope:- 0.001,762 i.e., an increase in the proportion responding of 17.62% for each 100 ppm of exposure

estimate of the standard error of the slope:- 0.000,611,8 i.e. 6.12% for each 100 ppm of exposure;

chi square for linear trend:- 7.888 which, with one degree of freedom, has a one-sided probability of only p = 0.002,49 i.e., indicating extremely high significance;

chi square for departure from linearity is only 0.131,407 which, with one degree of freedom, has a two-sided probability of as much as 0.716,9, clearly of no statistical significance.

I am indebted to Mr. Litt for having accessed the NCI computer programs aimed at determinig "virtually" safe levels of permethrin in the diet of the rats used in this study based on the response observed by the method of likelihood developed by Dr. Brown. The following are the estimates provided:-

Upper limit on the risk	"Virtually" safe levels (ppm) One-hit	Mantel-Bryan (log-probit)
1×10^{-8} or 1/100,000,000	0.000,002,2	0.000,64
5×10^{-8} or 5/100,000,000	0.000,008,8	0.001,2
1×10^{-7} or 1/ 10,000,000	0.000,022	0.001,6
5×10^{-7} or 5/ 10,000,000	0.000,088	0.003,3
1×10^{-6} or 1/ 1,000,000	0.000,22	0.004,4
5×10^{-6} or 5/ 1,000,000	0.000,88	0.009,9
1×10^{-5} or 1/ 100,000	0.002,2	0.014
5×10^{-5} or 5/ 100,000	0.008,8	0.033
1×10^{-4} or 1/ 10,000	0.022	0.050
5×10^{-4} or 5/ 10,000	0.088	0.13
1×10^{-3} or 1/ 1,000	0.22	0.21

The estimates given in the table above correspond to the 99% confidence limit; those corresponding to the 95% confidence limit are only 1.21 times larger for the one-hit procedure and only 1.34 times larger for the Mantel-Bryan approach.

The extrapolating slope for the Mantel-Bryan procedure is, of course, one probit per log dose. For the one-hit procedure the estimate for the slope was 0.002,143,729,1 which is quite close to the estimate of 0.001,762 mentioned for the linear trend analysis; At the 99% confidence limit, the upper limit on the extrapolating slope was 0.004,552 while that at the 95% confidence limit would be 0.003,760.

For the one-hit procedure the estimate of the spontaneous rate of positive animals was 2.587% while that for the Mantel-Bryan procedure was 2.262%.

The estimates given above are not totally inconsistent with those yielded by the second FMC mouse study carried out at Biodynamics:-

Those having reference to the Mantel-Bryan approach are 1.916 times larger than those arising out of the FMC version of the lung tumor data in their second mouse study conducted at Biodynamics; on the other hand, the one-hit estimates given in the table above are ~~6.827~~ 9.012 times smaller than those resulting from the lung tumor data in the same experiment (the FMC version of those data) and ~~9.012~~ 6.827 times smaller if one has reference to the Clement Associates version of those data.

In conclusion, it appears that the results emanating from this rat study confirm the findings arising out of the second FMC mouse study carried out at Biodynamics and they also seem to strengthen the conclusions reached for that mouse study:- that permethrin is without question a tumorigen with very low "virtually" safe levels of this agent corresponding to rather high upper limits on the risk.

Added to these impressions is the fact that Dr. Leonard Ritter of the Health Protection Branch, Government of Canada, has informed me last week by telephone that a very thorough analysis of the data emanating from the ICI rat study with permethrin has indicated similar results on the unquestionable tumorigenicity potential:- highly significant results with respect to meningiomas in both male and female animals and primary mammary tumors amongst female animals. Dr. Ritter also informed me that the results of the ICI mouse study, whose analysis was still in progress at the time of his call, seem likely to yield similarly positive conclusions on the tumorigenicity of permethrin. I expect to have considerable more details on the Canadian reviews of these two studies late next week when I plan to visit Dr. Ritter and his group in Ottawa, and, of course, I shall report my impressions to you.

It appears, therefore, that the conclusions that were presented to the SAP last March both by various members of your Branch and myself and which were also echoed by Dr. Tarone's letter of April the 7th last to Mr. Gray, the Executive Secretary of the SAP, seem to be shored up by these latest revelations.

cc:- Burin
Litt
Critchlow
Gee
McGrath
Johnson
Toxicology Branch files