Two Year Oral (Diet) Toxicity / Carcinogenicity Study of Fluorochemical FM-3924 in Rats

Riker Experiment No. 0281CR0012

Review by Dr William H Butler

At the request of 3M Corporate Toxicology, I have reviewed the above study with specific regard to the evidence of carcinogenicity of FM-3924. I have reviewed the study report including the individual histopathological diagnoses of Dr R Geil, study pathologist. I have not reviewed the individual pathological slides of the study.

Concern has been expressed over the findings of hepatocellular adenomas and carcinomas in female rats receiving 100 ppm FM-3924.

Results:

There are significant dose dependent reductions of body weights of 20.8% high dose,15.3% mid-dose and 3.5% low dose group female rats. There is no effect upon mortality. At 1 year there is a significant increase of liver weights in the high dose group.

Of the major non-neoplastic findings reported, hepatocyte megalocytosis (hypertrophy) was reported in 88% of high dose rats and 0% in the controls. Hyperplastic nodules were observed in 1 control and 9 high dose female rats. In males, megalocytosis was recorded in the treated groups and hyperplastic nodules in both the high dose group (10%) and mid dose group (2%).

Of the neoplastic findings, hepatocellular carcinomas were recorded in all male groups with no evidence of an increase associated with treatment. No adenomas were seen in any male group. In females hepatocellular adenomas and carcinomas were only observed in the high dose group.

	Control	High 100 ppm
Adenoma	0	4
Carcinoma	0	3

Conclusion:

The excessive reduction of body weight gain seen in both male and female highj dose rats is an indication that the MTD had been exceeded in both sexes. The megalocytosis or hypertrophy of hepatocytes is evidence of metabolic induction. Hepatocyte hypertrophy, following induction, is well recognised as a proliferative stimulus for hepatocytes. A long term sequela of this hypertrophy is recognised as hepatcyte degeneration reported in this study as cystoid degeneration. Further evidence of hepatocyte damage is the presence of hyperplastic nodules. Hyperplastic nodules are a reparative proliferative response to chronic liver injury. From this study it can be seen that at doses in excess of the MTD, there is chronic hepatocyte injury leading to a proliferative response.

In addition to the evidence of chronic liver injury discussed above, in the female high dose group both hepatic adenomas and carcinomas were observed. When considered individually neither achieve significance. It is, however, necessary to consider the combined incidence of adenomas and carcinomas as it has been suggested that the two lesions may represent a continuum; a suggestion which in my opinion is not justified. In the absense of genotoxicity, it is now clearly recognised that a chronic hepatocyte profilerative stimulus, as evidenced by continued hepatocyte injury, may be associated with the development of a neoplastic response. In the absense of chronic hepatic injury no neoplastic response is seen; the observation of this study.

In my opinion the marginal increase of the combined incidence hepatic adenomas and carcinomas observed in this study is secondary to the chronic hepatic effects of FM-3924 at doses in excess of the MTD.

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