

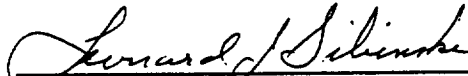
REPORT AMENDMENT NO. 1

TWO YEAR ORAL (DIET) TOXICITY/CARCINOGENICITY
STUDY OF FLUOROCEMICAL FM-3924 IN RATS

Experiment No.0281CR0012

The attached pages include revisions in the first paragraph on page 3 of the Summary and in the third paragraph of page 22 of the Discussion. The revisions were made to clarify that the incidence of benign hepatic adenomas found in the high-dose females was not statistically significant, although it was outside the historical limit.

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The overall incidence of hepatocellular adenomas and carcinomas was low in both control and FM-3924-treated groups with the high-dose female rats having a tumor incidence that, while not statistically significant, was outside historical control limits. The majority of neoplasms were observed in endocrine or endocrine-sensitive organs which are typical neoplastic sites for older rats of this strain. The incidence of these neoplasms was similar among control and test article-treated groups, and did not demonstrate a unique tumor type.

Based on tumor incidence, types of tumors, onset time of tumor appearance, malignancy patterns of tumors and the final mortality values at two years, FM-3924 was not considered to be carcinogenic in the rat under the design and conditions of this study.

parameters that were progressive over time. These findings were considered to be associated with the progressive degenerative changes of naturally occurring chronic renal disease commonly found in rats of this strain.

The primary test article effect occurred in the liver as increased organ weight (both absolute and relative), as gross findings at necropsy, and as histopathologic alterations. These changes were observed at the one year necropsy, but showed remarkably little progression one year later at the two year necropsy. The high-dose males and females had essentially equal incidences of hepatic findings, while the mid- and low-dose males were more markedly affected than were the females from the corresponding dose groups.

Hepatomegalocytosis and hepatocellular vacuolation are characteristic of increased metabolic activity in the rat. It is recognized that these lesions may progress to cystoid degeneration and, ultimately, hepatocellular necrosis. The incidence of hepatic necrosis in this study was slightly increased only in the high-dose males. Since the liver in the rat rarely repairs parenchymal cell loss with fibrosis or scar tissue, a more typical cellular reaction is hepatocellular hyperplasia. In this study, the incidence of hyperplastic nodules were increased only in the high-dose male and female animals (ie., 10% and 18%, respectively) compared to the control groups (ie. 0% and 2%, respectively). It is important to note that no proliferative hepatic lesions (ie. hyperplasia nor neoplasia) were seen in any of the high-dose rats after receiving FM-3924 for one year.

Primary liver neoplasms observed in this study after two years consisted of hepatocellular adenomas and carcinomas. The overall incidence of these neoplasms was low, with carcinomas occurring in both the control and FM-3924 treated groups as follows: males 6%, 4%, 2% and 2%; and females 0%, 6% 0% and 0% for the control, high-, mid- and low-dose groups, respectively. Benign hepatic neoplasms (ie. adenomas) were not found in any group except the high-dose females where, although not statistically significant, an incidence of 8% was recorded. Considering the chronic liver stimulation noted in both the high-dose male and female groups during their life span, the incidence of hepatic neoplasia appears to be within reasonable limits with the possible exception of the high-dose female group. Combined malignant and benign incidence values are within

reasonable historical control limits for the high-dose males while the high-dose females appear to be slightly outside these limits only because there were no liver tumors seen in the control group. Based on these findings, FM-3924 was not considered to be a hepatic carcinogen in the rat.

Most of the neoplasms observed in this study originated from endocrine or endocrine-sensitive organs including the adrenal glands, mammary gland, pituitary, thyroid and uterus. These are common sites for spontaneous or naturally occurring oncogenesis in this strain of rat as evidenced by the specific tumor incidence in the control group (see Table 19). Deviations from the control incidence for these neoplasms were neither numerically meaningful nor did they involve a unique tumor type not commonly seen in this strain of rat.

The non-neoplastic findings reported from the histopathologic evaluation of all of the animals scheduled for the two year necropsy were mostly geriatric lesions typical for this strain of rat. The organs in which these lesions were found included adrenal glands, heart, kidneys, lung, testes, ovaries, thyroid, urinary bladder and uterus. Specific deviations from the control incidence seen in FM-3924 treated groups were addressed in the results section of this report. However, the following changes were considered equivocal test article related effects. The incidence of nodular hyperplasia of the adrenal cortex was significantly increased (22%) in the high-dose males compared to the same finding in the controls (4%), while the high-dose female rats showed a much lower incidence (2%).

Lung changes were also sporadic in occurrence with the incidences of the accumulation of alveolar macrophages increased in the high-dose males and females. The incidence of ovarian (stromal) tubular hyperplasia was increased in a statistically significant and dose dependent manner. The interpretation of this finding is uncertain, but a possible explanation is that it was secondary to the hepatic changes which may evoke endocrine related effects in older rats. Likewise, the increase in uterine cystic glands in the high-dose females could be a manifestation of this biological phenomenon.