DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administrati n

Memorandum

Date: August 29, 2002

From: Director, Division of General Scientific Support

Subject: Fluorochemical FC-143 Study in Rats - Comments

To: Michelle Twaroski, Ph.D.
Office of Food Additive Safety, HFS-275

As per your request, I have reviewed the contractor's review report of the "Two Year Oral (Diet) Toxicity/Carcinogenicity Study of Fluorochemcial FC-143 in Rats". I also referred to the sponsor's original study report, the CD-ROM version of which you had provided me earlier.

Briefly, fluorochemical FC-143 was administered in the diet to male and female Sprague-Dawley (SD) rats for two years at doses of 0, 30, or 300 ppm. Survival was generally good in all dose groups in both males and females. However, the high dose males had significantly better survival than the control or low-dosed male groups. The survival was comparable among females. In rats treated with 300 ppm, there was an overall decrease in mean body weight gain in both males (5% lower than controls) and females (14% lower than controls).

I focused my attention to the histopathologic findings and primarily to the neoplastic and related findings reported in the liver, testis, mammary gland and thyroid.

Liver:

There are treatment related histopathologic changes reported in the liver in both male and female rats. The non-neoplastic findings included megalocytosis, cystoid degeneration and portal mononuclear cell infiltration. Megalocytosis was reported only in the treated animals in both males (0/50, 6/50, 40/50) and females (0/50, 1/50, 8/50) with increased severity of the lesion in the high dose group. Megalocytosis was described in the sponsor's report as a lesion characterized by an increase in size of hepatic parenchymal cells due to increased cytoplasmic volume. Cystoid degeneration was considerably increased in high dose males (4/50, 7/50, 28/50). The incidence of cystoid degeneration in female rats was reported minimal, one animal each in the low and high dose groups. Portal mononuclear cell infiltration was also reported increased in the high dose males compared to the control group (37/50, 32/50, 48/50) with slightly increased severity in the high dose group. However, the latter lesion is quite common and highly variable in its incidence. Overall, it appears that megalocytosis in treated rats of both sexes and cystoid degeneration in high dose males are treatment related. The increases in some of the liver enzymes and slight increase in liver weights in the treated animals may be related to these lesions.

The proliferative lesions reported in the liver were hyperplastic nodules and hepatocellular carcinomas. The incidence of hyperplastic nodules was slightly increased in the high dose

group of males (0/50, 0/50, 3/50) and females (1/50, 0/50, 2/50). Hyperplastic nodule was defined in the sponsor's report as a localized proliferation of hepatic parenchymal cells. Hepatocellular carcinomas were increased slightly in the high dose males (5/50) compared to the controls (3/49) or low dose (1/50). In females, hepatocellular carcinoma was reported in one animal in the high dose group only. The sponsor's report does not state whether hepatocellular adenomas were noted or not. The study was conducted in the early 80s. In the past, it was not uncommon to use the terms hepatocellular carcinoma and hyperplastic nodules but not the term hepatocellular adenoma. Lesions formerly diagnosed as hyperplastic nodules would probably be classified as either foci of cellular alteration or hepatocellular adenomas, based on current morphologic criteria.

Based on the histopathological findings reported in the liver, it can be stated that there is an increase in proliferative hepatocellular lesions in the high dose males (hepatocellular carcinomas plus hyperplastic nodules 8/50 (16%) vs. 3/49 (6%), suggesting a treatment related effect. The increased incidence of non-neoplastic findings in the liver is further evidence that this is a target organ.

Testis

Leydig cell adenomas are increased in both the low (2/50) and high dose (7/50) groups compared to control group (0/50). In addition, the incidence of Leydig cell hyperplasia was reported as (0/49, 2/50, 1/50) in the control, low dose and high dose groups, respectively. Leydig cell tumors can occur as spontaneous lesions in SD rats but at a very low incidence. The average background incidence of Leydig cell tumors in this strain of rat is reported as 6.5%, range indicated as 1.4 – 13.3% (McMartin et al. Tox Path.1992, vol. 20 (2), 212-225.)

Mammary gland

Four types of mammary tumors were reported in females: adenoma, fibroadenoma, adenocarcinoma, and carcinoma. The incidence of fibroadenoma was reported as (10/46, 22%; 19/45, 42%; 21/44, 48%) in the control, low dose and high dose groups, respectively. The incidence of adenocarcinoma was reported as (7/46, 15%; 14/45, 31%; 5/44, 11%) in the control, low dose and high dose groups, respectively. In addition, three adenomas and one carcinoma were reported only in the control group. Looking at the combined incidence figures of fibroadenomas and adenomas, there appears to be a dose related increase in the occurrence of benign tumors. It is, however, appropriate to evaluate the combined incidence of benign and malignant tumors. When this is done, there is no apparent dose relationship of mammary tumors to treatment. There are more mammary tumors in the mid dose group than the control or the high dose groups. There was no indication of any increase in the lobular hyperplastic lesions in any of the groups, control or treated. Mammary tumors in SD rats occur quite frequently as spontaneous lesions (McMartin et al., reference cited above). The incidence of mammary tumors in this study does not appear to be treatment related.

Thyroid

In males, there was a slight increase in C cell adenomas in treated animals compared to

controls. The incidence of C cell adenomas were reported as (0/43, 0/47, 4/47) in the control low dose and high dose groups, respectively. However, two animals with C cell carcinomas were reported in the control group. C cell tumors are fairly common in SD rats and the incidence of C cell tumors (benign plus malignant combined) appears to be well within the background control range of these lesions.

In summary: liver and testis appear to be the target organs in this study. In the liver, there was reported an increase in hepatocellular lesions (hepatocellular carcinomas plus hyperplastic nodules) particularly in the high dose males. The incidence of Leydig cell tumors in the testis is also very suggestive of a treatment related effect.

Let me know if you have any questions.

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