3M MEDICAL DEPARTMENT

TOXICOLOGY SERVICES

To: Georjean Adams 290-4-01

cc: John Butenhoff 220-2E-02

From: Marv Case 220-2E-02

Subject: FC 95 and 143 Teratology

Date: 26 May 1998

John passed on to me your request for someone to review and write an analysis on the eye lens defect that was reported in the original FC 95 rat teratology study. I have reviewed the toxicology study files on FC 95 and FC 143. Attached are my review comments and conclusions. You will note that the lens defect reported was subsequently shown to be a sectioning artifact and was not observed in latter teratology studies done at other laboratories. To date, teratogenic effects have not been shown with either compound at doses which are not maternally toxic

Additional FC teratology studies are to be started soon. A FC 95 rabbit teratology study (we have no rabbit data), a rat FC 10 teratology study (we need to determine an NOEL level), and a rabbit FC 10 teratology study (we have no rabbit data) have been contracted and should start in June/July.

Review of FC 95 & 143 Teratology Studies

FC 95

A rat FC 95 teratology study (study no. 0680TR0008) was conducted at Riker Laboratories and the study report is dated Dec. 1980. Dose levels (oral) given to the pregnant rat dams were 0, 1, 5, and 10 mg/kg. Maternal toxicity (reduced weight gain) occurred at the high dose of 10 mg/kg. Evidence of fetal toxicity was not found at any dose level. No skeletal and soft tissue teratogenic changes were found at any dose level with one exception. A change in the lens of the eye was found in all dose groups including the control but the incidence in high dose group was significantly higher. This change was reported out as developmental eye abnormality and the summary of the report states the compound was teratognic.

Another rat FC 95 teratology study (study no. 154-160) was done at Hazleton Laboratories and the study report is dated Nov. 1983. Dose levels (oral) given to the pregnant dams were 0, 1, 5, and 10 mg/kg (same dose levels as in the previous rat teratology study). Maternal toxicity was found at the higher two dose levels – 5 & 10 mg/kg. Signs of maternal toxicity were reduced weight gain, anorexia, thinness, and death of two of the high dose (10 mg/kg) dams. Fetal toxicity (increased uterine loss of pups at 10 mg/kg and reduced pup weights at 5 & 10 mg/kg) which was related to the maternal toxicity was observed at the higher two dose levels. Pup examination revealed delayed ossification at the high dose as well as visceral anomalies of cleft palate and crytorchism. The study concluded that the compound did not appear to be teratogenic at dose levels less than or equal to 5 mg/kg. An important finding was no eye or lens abnormality at any dose level.

I can not find any record of a rabbit teratology study being done on FC 95. (Note we have just contracted for a rabbit FC 95 teratology study; should have data by the end of 1998.)

FC 143

A rat FC 143 teratology study (study no. 0681TR0110) was conducted at Riker Laboratories and the study report is dated Dec. 1981. Dose levels (oral) given to the pregnant rat dams were 0, 0.05, 1.5, 5, and 150 mg/kg. Maternal toxicity (reduced weight gain and three deaths) occurred at the high dose of 150 mg/kg. Evidence of fetal toxicity was not found at any dose level. Although delayed ossification was found in the high dose pups (related to maternal toxicity), no skeletal and soft tissue teratogenic changes were found at any dose level. As was the case in FC 95 rat teratology study, a change in the lens of the eye was found in all dose groups including the control but the incidence in high dose group was significantly higher. However, in this study report this finding is

attributed to an artifact created by sectioning of the eye. The study conclusion is that the compound was not teratogenic.

An outside consultant and teratology expert, Dr E. Marshall Johnson from Jefferson Medical College, visited 3M and reviewed the rat pup eye specimens in question from the two Riker rat teratology studies. He concurred that the eye/lens changes were, in fact, sectioning artifacts and not compound related teratology abnormalities.

A rabbit FC 143 teratology study (study no. 0681TB0398) was conducted at Riker Laboratories and the study report is dated Feb. 1982. Dose levels (oral) given to the pregnant rabbit dams were 0, 1.5, 5, and 50 mg/kg. Maternal toxicity (reduced weight gain) occurred at the high dose of 50 mg/kg. True fetal toxicity was not found at any dose level but high dose pups had slightly increased incidence of rib variations which was attributed to embryotoxicity. No skeletal and soft tissue teratogenic changes were found at any dose level. The study conclusion is that the compound was not teratogenic.

Staples and co-workers at DuPont Haskell Laboratories have done additional rat teratology studies on FC 143. In one study, pregnant rat dams were dosed orally at 0 and 100 mg/kg (report dated Jan. 1982). In other study, pregnant rat dams were exposed to inhalation doses of 0, 0,1, 1.0, 10 and 25 mg/m^3 (report dated Jan, 1982). These repeat studies did not reveal any eye or lens abnormalities in rat pups. This work has been published and the reference is: Staples RE, Burgess BA, Kerns WD: The embyro-fetal toxicity and teratogenic potential of ammonium perfluorooctanoate (APFO) in the rat. Fund Appl Toxicolo 4:429-440, 1984.

Conclusion

Thus, the weight of the evidence indicates that neither FC 95 nor FC 143 causes teratogenic effects in animals when dosed at levels which are not maternally toxic. Even at maternally toxic doses, effects seen in the pups were those generally associated with maternal toxicity. The lens change observed in rat pups in Riker Laboratories studies was a sectioning artifact and was not found upon repeat studies at independent laboratories.

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