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3M

February 25, 1999

Mr. Terry R. O'Bryan  
United States Environmental Protection Agency  
401 M Street SW  
Washington, DC 20460

Dear Mr. O'Bryan:

Attached is a summary put together by Dr. Marv Case, a 3M corporate scientist and a member of our Toxicology staff. He summarizes our approach to understanding of the studies that you cited during our visit in December.

It is my understanding that we will probably have more face to face meetings in the future, and if that occurs we can certainly make the reproductive and developmental data a subject of one of those meetings.

Please contact me if you'd like any further information.

Regards,

*Larry R. Zobel*

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Staff Vice President & Medical Director

LRZ:jme  
Attachment

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## FC Rat Teratology Study Results

Larry Zobel requested this summary/review in response to comments made in a EPA Status Report on BEHQ-1180-0373S, BEHQ-1180-0374S, BEHQ-0281-0373S Supplement and BEHQ-0281-0374S Supplement which sent from Frank D. Kover to Joseph J. Merenda. This EPA document concerns rat teratology study results on 3M fluorochemicals. In the third paragraph of the report the following is stated: "...while FC-95 did not produce an increase in skeletal abnormalities, the mixture of perfluoroethanol derivatives produced cleft palates in the high dose and mid dose groups (significant in the high dose group), blood in the fetal kidney parenchyma in all three groups (significant in the high dose) and malformations in fetal sternbrae and other skeletal aberrations of varying significance at different dose levels. The final report also states that FC-95 at the high dose and the perfluoroethanol derivative mixture were maternally toxic in reducing weight gain during dosing but did not affect the ovaries or reproductive tract contents of the dams and were not embryotoxic."

While the above quoted text from the EPA document says FC-95, it appears that the results referred to were those found on two 3M fluorochemicals. One chemical is perfluorooctanesulfonate (FC-95) and the other chemical is 2-(N-ethyl perfluorooctanesulfonamido)-alcohol.

### Perfluorooctanesulfonate (FC-95)

Two rat teratology studies have been done with perfluorooctanesulfonate (FC-95). The first study was a Riker Study (study number 0680TR0008); and the final report is dated 18 December 1980. The other study was done at Hazleton Laboratories (study number 154-160); and the final report is dated 22 November 1983. The oral dose levels in both rat teratology studies were the same, namely 0, 1, 5, and 10 mg/kg/day. In the Hazleton study, there was maternal toxicity at the higher two dose levels (5 & 10 mg/kg/day). Two high dose females died and there was reduced body weight gain along with reduced food consumption at the higher two dose levels. A slight increase in number of in-utero resorption sites in the high dose dams was another indication of maternal toxicity. In the Riker study only the high dose (10mg/kg/day) females had reduced body weights.

3M uses the widely accepted classification of alternations found in a teratology study. Variations which are non-permanent and common findings in controls (non-teratogenic events). Reversible delays in development which are usually delays in ossification. These developmental delays are frequently seen at maternal toxic doses and are a reflection of the maternal toxicity in the fetuses. Malformations which are irreversible changes that occur at low incidence in controls (teratogenic events). Malformations can be further subdivided into two categories – those related to dam toxicity or those that occur at non-toxic dose. In regard to potential human risk, the latter are of more concern as they represent a fetal effect at non- toxic maternal dose.

In the Hazleton perfluorooctanesulfonate (FC-95) rat teratology study, increased incidence of cleft palate (a teratogenic event) was found at the high dose (10 mg/kg/day). One mid dose fetus had a cleft palate but this does not indicate a teratogenic finding as a low incidence of cleft palate can be seen in control rat fetuses. The high dose of 10 mg/kg was clearly toxic to the dams. There was two high dose dam deaths as well as a rather profound reduction in body weight gain of the high dose dams.

Increased incidence of cleft palate in rodent teratology studies has been related to dam toxicity. This relationship was reported a number of years ago in mice <sup>1</sup> in regard to maternal stress and subsequently shown to occur at toxic doses in mouse teratology studies on chemicals. <sup>2</sup> An extensive 1985 review of animal teratology study results revealed that a similar relationship existed in rats. That is, increased incidence of cleft palate in rat fetuses was associated with maternal toxicity. <sup>3</sup>

No cleft palates were found in the Riker perfluorooctanesulfonate (FC-95) rat teratology study even though the high dose was the same (10 mg/kg/day) as in the Hazleton. However, the degree of dam toxicity was less in the Riker study. There were no high dose dam deaths and the body weight effect, although present, was of less severity.

Note in the Riker study a lens abnormality was found in all dose groups and was reported as a teratogenic effect. But subsequent examination of the lens sections by E. Marshall Johnson, consultant expert teratologist, revealed that the lens change was a sectioning artifact. A copy of Marshall Johnson's letter report is attached to the EPA status report. The EPA reviewer did not mention the lens change in his summary and it would appear that Marshall Johnson's explanation was acceptable.

In both perfluorooctanesulfonate (FC-95) rat teratology studies at higher dose levels, there was some increased incidence of delayed ossification and skeletal variations (which also can be increased at maternal toxic doses). But there no skeletal malformations (teratogenic events) in either study. Thus, the fetal alterations found in both rat teratology studies on perfluorooctanesulfonate (FC-95) can be related to maternal toxicity.

#### 2-(N-ethyl perfluorooctanesulfonamido)-alcohol

Oral rat teratology on 2-(N-ethyl perfluorooctanesulfonamido)-alcohol was the subject of Riker study number 0680TR0010; final report is dated January 22 1981. (Note in the report 2-(N-ethyl perfluorooctanesulfonamido)-alcohol is referred to as FM-3422.) Dose levels for the study were 0, 25, 37.5, and 75 mg/kg. Maternal toxicity was manifested at the high dose as markedly reduced body weight gains, clinical signs of toxicity (lethargic, thinness, blood in stool) and three deaths. A definite and significant reduced body weight gains occurred at the mid dose. The low dose group also had reduced weight gain but the difference from controls was not statistically significant. Thus, maternal toxicity was definite at the higher two dose levels and probable at the low dose. One could make the judgement that the dose levels used in the study were too high and lower dose levels would have been more appropriate.

An increased incidence of cleft palate was found in the high dose fetuses but as indicated above increased cleft palate is a reflection of dam toxicity. Skeletal aberrations in sternbrae and vertebrae as well as increase in non-ossified site were observed in the fetuses. Although some of these skeletal changes were indicated as teratogenic events in the report, we now know that these fetal skeletal manifestations are associated with dam toxicity. Blood in fetal kidney parenchyma is a fetal variation and not indicative of a teratogenic event. It is a reflection of how the fetus was handled during removal from the uterus at Cesarean section of the dam.

In summary, the fetal aberrations found in the oral rat teratology studies with 3M fluorochemicals [(perfluorooctanesulfonate - FC-95) and 2-(N-ethyl perfluorooctanesulfonamido)-alcohol], occurred at maternal toxic doses and were a reflection of maternal toxicity. No true teratogenic effects occurred at non-toxic maternal dose levels.

*Marvin T Case*  
Marvin T. Case DVM, PhD  
Corporate Scientist  
3M Corporate Toxicology

*10 Feb 1999*  
Date

## References

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- <sup>1</sup> Barlow SM, McElhatton PR, Sullivan RM: The relationship between maternal restraint and food deprivation, plasma corticosterone, and induction of cleft palate in the offspring of mice. *Teratology* 12:97-104, 1975.
- <sup>2</sup> Khera KS: Maternal toxicity – A possible factor in fetal malformations in mice. *Teratology* 29:411-16, 1984.
- <sup>3</sup> Khera KS: Maternal Toxicity: A possible etiological factor in embryo-fetal deaths and fetal malformations of rodent-rabbit species. *Teratology* 31:129-53, 1985.