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NOTE TO FILE - OPPTS 50639

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FROM: Karen Lannon

SUBJECT: Revised PFOS Hazard Assessment

Attached is a revised PFOS Hazard Assessment. Minor changes from the text in the original version (August 31, 2000) are found on pages 6, 7, and 26, and concern the corrected 1974 reference to Bieseimer and Harris. The conclusions were not affected by these changes.

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Hazard Assessment and Biomonitoring Data on Perfluorooctane Sulfonate - PFOS

I. Executive Summary

In human blood samples, PFOS has been detected in the serum of occupational and general populations in the ppm to ppb range. In the U.S., recent blood serum levels of PFOS in manufacturing employees have been as high as 12.83 ppm, while in the general population, serum collected from blood banks and commercial sources have indicated mean PFOS levels of 30-44 ppb. Levels in a very small sample of children yielded even higher results, with a mean level of 54 ppb.

Sampling of several wildlife species from a variety of sites across the United States has shown widespread distribution of PFOS. In recent analyses, PFOS was detected in the ppb range in the plasma of several species of eagles, wild birds, and fish. Endogenous levels of PFOS have also been detected in the ppb range in the livers of unexposed rats used in toxicity studies, which presumably occurred through exposure to a dietary source (fishmeal).

Studies show that PFOS is well-absorbed orally and distributes mainly in the serum and the liver. No further metabolism is expected. Elimination from the body is slow and occurs via the urine and feces. Serum PFOS levels in 3 retired male 3M chemical workers have been followed for five and a half years and suggest a mean elimination half-life ($t_{1/2}$) of 1,428 days (approximately 4 years). Based on the pharmacokinetic data obtained from a 28-day oral study in male and female monkeys, a volume of distribution (V_d) of 0.19L/kg was reported; no sex differences in the pharmacokinetic parameters were noted.

PFOS has shown moderate acute toxicity by the oral route with a rat LD50 of 251 mg/kg. A one-hour LC50 of 5.2 mg/l in rats has been reported. PFOS was found to be mildly irritating to the eyes and non-irritating to the skin of rabbits. PFOS was negative in mutagenicity studies in five strains of salmonella and did not induce micronuclei in an *in vivo* mouse bone marrow micronucleus assay.

Numerous repeat-dose oral toxicity studies on PFOS have been conducted in rats and primates. Adverse signs of toxicity observed in rat studies included increases in liver enzymes, hepatic vacuolization and hepatocellular hypertrophy, gastrointestinal effects, hematological abnormalities, weight loss, convulsions, and death. These effects were reported at doses of 2 mg/kg/day and above. Adverse signs of toxicity observed in Rhesus monkey studies included anorexia, emesis, diarrhea, hypoactivity, prostration, convulsions, atrophy of the salivary glands and the pancreas, marked decreases in serum cholesterol, and lipid depletion in the adrenals. The dose range for these effects was reported between 1.5-300 mg/kg/day. No monkeys survived

beyond 3 weeks into treatment at 10 mg/kg/day or beyond 7 weeks into treatment at doses as low as 4.5 mg/kg/day. At doses as low as 0.75 mg/kg/day, cynomolgus monkeys exhibited low food consumption, excessive salivation, labored breathing, hypoactivity, ataxia, hepatic vacuolization and hepatocellular hypertrophy, significant reductions in serum cholesterol levels, and death.

Postnatal deaths and other developmental effects were reported at low doses in offspring in a 2-generation reproductive toxicity study in rats. At the two highest doses of 1.6 and 3.2 mg/kg/day, pup survival in the first generation was significantly decreased. All first generation offspring (F1 pups) at the highest dose died within a day after birth while close to 30% of the F1 pups in the 1.6 mg/kg/day dose group died within 4 days after birth. As a result of the pup mortality in the two top dose groups, only the two lowest dose groups, 0.1 and 0.4 mg/kg/day, were continued into the second generation. The NOAEL and LOAEL for the second generation offspring (F2 pups) were 0.1 mg/kg/day and 0.4 mg/kg/day, respectively, based on reductions in pup body weight. Reversible delays in reflex and physical development were also observed in this study, raising concerns about the potential for developmental neurotoxicity following exposure to PFOS.

Developmental effects were also reported in prenatal developmental toxicity studies in the rat and rabbit, although at slightly higher dose levels. Signs of developmental toxicity were evident at doses of 5 mg/kg/day and above in rats administered PFOS during gestation. Significant decreases in fetal body weight and significant increases in external and visceral anomalies, delayed ossification, and skeletal variations were observed. Abnormalities of the lens of the eye were also reported at doses as low as 1 mg/kg/day in one rat prenatal developmental study, but could not be repeated in a second study of similar design. At doses of 2.5 mg/kg/day and above, significant reductions in fetal body weight and significant increases in delayed ossification were observed in rabbits administered PFOS during gestation.

There are several uncertainties in the data-base. For example, since the two-generation reproductive toxicity study dosed the F0 males for only six weeks prior to mating and did not include any evaluations of sperm number, motility, and morphology, an analysis for the potential for male reproductive toxicity is incomplete. Although blood concentrations of PFOS in animals have been estimated based on limited pharmacokinetic data, it is uncertain how PFOS was assayed in these analyses. Moreover, the extent of potential interspecies and intraspecies variability in the pharmacokinetic handling of PFOS is not well understood and cannot be fully ascertained with the two-generation toxicity study alone. There presently exists uncertainties with the human exposure data as well. Data on exposure pathways for all populations is missing. For occupational exposures, only limited data on the sampled workers is available and human serum levels were not measured over time in the same individuals. Data on general population exposures come from pooled sera and must be interpreted with caution. In addition, due to the long half-life of PFOS in the body and given the limited knowledge regarding the distribution of PFOS in the body, it is uncertain whether body burden is adequately reflected by serum levels. Several on-going mechanistic and other studies may help address some of these data needs.