APPENDIX A

Mechanisms of Action Associated with PFOA in Addition to Peroxisome Proliferation

Thyroid Hormones

Since 1978, studies have documented damage to the thyroid gland following exposure to PFOA and chemicals that break down into PFOA, in monkeys and other animals (1-7). The damage includes cellular effects on the thyroid and hypothyroidism, a condition characterized by low levels of thyroid hormones that control growth and metabolism and that are critical for proper brain development. The cellular changes seen in response to PFOA are the same type caused by a prolonged state of hypothyroidism and are also associated with developing thyroid tumors in rodents (8,9). Similarly, in 1998, 3M scientists published a study that included a table showing that workers with high blood levels of PFOA had statistically significant increases in TSH (10). Unfortunately, the thyroid was not collected in the recent reproduction study (11, 12).

Thyroid cancer and hypothyroidism are current public health concerns. An estimated 10 million people, mostly women, in the US have hypothyroidism (13). The condition is of particular concern for pregnant women because thyroid hormones are critical for proper brain development in the fetus. Small reductions in maternal thyroid hormone levels during pregnancy have been associated with reduced IQs in children. Incidence rates of thyroid cancer in both women and girls have been increasing in the US during the past decade (14, 15). An underactive thyroid gland in adults can lead to fatigue, depression, anxiety, unexplained weight gain, hair loss, and low libido. More serious, however, are the effects of thyroid hormone disruption for the developing fetus and child. Fetuses, infants and children who experience significant changes in hormone levels may suffer mental retardation, loss of hearing and speech, abnormal testicular development or deficits in motor skills. In older children, depressed thyroid levels have been associated with lower motivation to learn and attention deficit disorder (16, 17).

Much more research needs to be done to investigate the different effect of PFOA on the thyroid over time, however, it is clear that some relationship exists between PFOA and the thyroid.

Gap junction cellular communication (GJIC)

PFCs, such as PFOA (C8) and PFDA (C10), can attack cell membranes, causing cells to swell and eventually burst (18). In cells that are not destroyed, PFOA can inhibit gap junction intercellular communication (GJIC) (19, 20). PFOA inhibited GJIC at concentrations of at less than 100µM (< 500 ppb). Decreased GJIC is a recognized tumor promoting action. A wide range of PFCs inhibit GJIC and the effect being more dependent of the length of the fluorinated tail rather than functional group type (19). PFCs with carbon lengths ranging from C5 to C16 inhibit GJIC, and among this group, C6 to C10 PFCs are the most potent (19, 20).

Mitochondrial function/Membrane disruption
PFOA, like other perfluorochemicals (PFCs), causes mitochondrial toxicity. At concentrations in the \( \mu M \) molar ranges, PFOA can cause changes in mitochondrial consistent with "induction of a slight increase in intrinsic proton leak of the mitochondrial inner membrane due to changes in its fluidity, which is a surfactant-like effect of these agents" (21). Other studies have found that PFOA can uncouple oxidative phosphorylation (22, 23) and induces more severe cellular toxicity in oxygen rich portions of the liver (23).

Damage to mitochondrial function can cause "wasting syndrome" and has been implicated in many human diseases, including diabetes, Parkinson's disease and heart disease. A study conducted in human liver cells (HepG2) found that mitochondrial damage (and generation of oxygen species) underlies PFOA induced liver cell apoptosis.

**Increased estradiol**

PFOA increases production of estradiol, a potent form of estrogen, by increasing activity of the enzyme that converts testosterone to estradiol (aromatase) (24, 25). It is thought that estradiol-stimulated transforming growth factor-alpha (TGF-\( \alpha \)) levels are a risk factor for pancreatic acinar and Leydig cell tumors (OPPTS, 2003). Biegel et al. (24) also found that PFOA increased testicular levels of estradiol. While female rats have not been studied as often as male rats, studies have shown that estradiol stimulates excess release of TGF-\( \alpha \) in mammary cells. Because high levels of estrogen are a risk factor for Leydig cell tumors by PFOA (25), USEPA has suggested that the induction of Leydig cell tumors, a type of testicular tumor, by PFOA may be endocrine mediated, possibly by sustained elevation of estrogen or the inhibition of testosterone biosynthesis.

**REFERENCES**


4) DuPont Haskell Laboratory. 2002a. Developmental and one-generation reproduction study: Mixture of poly(difluoro-methylene), alpha-fluoro-omega[2-(phosphonoxy) ethyl]-, monoammonium salt (CAS# 65530-71-4); poly(difluoro-methylene), alpha-fluoro-omega[2-(phosphonoxy) ethyl]-, diammonium salt (CAS# 65530-72-5); poly(difluoromethylene), alpha, alpha'-[phosphinicobis(oxy-2,1-ethanediyl)bis [omega-fluoro-], ammonium salt (CAS# 65530-70-3); isopropyl alcohol (CAS# 67-63-0); and water (CAS#
7732-18-5). U.S. Environmental Protection Agency; Toxic Substance Control Act (TSCA) Section 8(e) Submission 8EHQ-1202-15247A. December 20, 2002.


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