APPENDIX F

A comparison of a review of Animal studies on fluoride's reproductive effects by Stan Freni (1994) and the DHHS (1991). Note: Freni's review was originally written for the DHHS (1991) report but according to Freni was "watered downto avoid alarming the public."

FRENI (1994)

When a bioassay showed that fluoride added to the drinking water might be carcinogenic to rats (NTP, 1990) the US PHS conducted a comprehensive review of the risk and benefits associated with water fluoridation (Committee to Coordinate Environmental Health and Related Programs, 1991). Among the consistent findings was that fluoride may affect reproduction in animals. Rats exposed to 430 ppm dietary fluoride showed anestrus with cumulative generational effect (Phillips et al., 1933). This was confirmed in a more recent study showing a smaller size in the second mating cycle of rats exposed to 460 ppm dietary fluoride (Marks et al,, 1984). Mice exposed to 100-200 ppm fluoride in water showed reduced fertility (Messer et al., 1973).

Heifers exposed to 5 ppm fluoride in water during 4 breeding seasons developed anestrus, with calving rates dropping to 30% of the normal rate (Van Rensburg & De Vos, 1966). At higher fluoride levels, the effect occurred earlier and was more severe. At 393-560 mg/d fluoride in the diet, milk production dropped, abortion rate and calf mortality increased, and there were congenital fluorosis and stunted postnatal growth (Eckerlin et al.,, 1986; Maylin et al., 1987). In a fox breeding farm, feed with up to 98 ppm fluoride caused pup mortality due to agalactia of the vixen, and the surviving offspring later produced smaller litters, which suggests permanent damage has occurred (Eckerlin et al., 1988). Poultry and birds of prey exposed to fluoride showed lower egg production, failure of the eggs to hatch, and/or increased chick mortality (Carriere & Bird, 1987; Hahn & Guenter, 1986; Hoffman, et al., 1985 Pattee et al., 1988).

Many studies have investigated how fluoride exerts its toxic effects. Fluoride easily crosses the placenta; fetal death and placental necrosis were noted after intraperitoneally injecting rats with 0.1 mg/d sodium fluoride (Armstrong et al., 1970; Caldera et al., 1988; DeVoto et al., 1972). At the molecular level, fluoride affects the G-proteins and thus, the adenyl cyclase system for signal transduction (Sternweis & Gilman, 1982), causing inhibition of enzymes involved in cell growth and protein synthesis (Holland, 1979; Song et al, 1988). This in turn might affect fertility by lowering the release of hormones and sperm motility (Groom et al., 1971; Tash & Mann, 1973). Reproductive toxicity may also result from maternal toxicity, such as weight loss and lower milk production (Eckerlin et al., 1986, 1988), and from paternal toxicity (Araibi et al., 1989; Chubb, 1985; Pati & Bhunya, 1987). At low exposure levels, the toxic effects of fluoride are more subtle: low birth weight, delayed fetal skeleton development, or retarded postnatal development (Hoffman et al., 19865; Maylin et al., 1987; Wheeler et al., 1988).

DHHS (1991)

IMPAIRMENT OF FERTILITY

Animal Studies

Adverse effects on reproduction were reported by Messer et al. (1973) who found reduced fertility in female Swiss Webster mice during 25-week studies with drinking water containing a concentrations of fluoride (as sodium fluoride) that were lethal (200 ppm) or caused significant decreased maternal weight gain (100 ppm). No effects on fertility of two generations of mice were seen with dams given water containing 50 ppm fluoride. Conflicting reports exist regarding spermatozoal abnormalities in mice resulting from fluoride treatment. Pati and Bhunya (1987) reported abnormal spermatozoa in Swiss mice given intraperitoneal injections of 8 mg of sodium fluoride/kg on 5 successive days. However, Li et al. (1987) reported no increases in sperm abnormalities in B6C3F1 mice given 5 daily oral doses of sodium fluoride at 70 mg/kg, and Dunipace et al. (1989) found no increase in abnormal sperm morphology in B6C3F1 mice maintained for 21 weeks on drinking water containing up to 75 ppm fluoride (as sodium fluoride). Mice given sodium fluoride in drinking water at concentrations of 500 or 1000 ppm for two to three months showed clear evidence of damage to spermatogenesis (Kour and Singh, 1980).

Male rat fed diets with added fluoride sufficient to give doses of 25 to 30 mg fluoride/kg body weight did not show adverse effects on reproductive organs or their function; female rats given equivalent doses of fluoride (0.043 percent of the diet) showed reduced diet consumption and suppression of estrus (Phillips et al., 1933). Sodium fluoride administered to male rats at dietary concentrations of 100 or 200 ppm for 60 days caused a dose-related decrease in reproductive performance; a decrease in serum testosterone levels was observed with the higher dose (Araibi, et al., 1989).

Aulerich et al. (1987) found no effects on reproduction of mink maintained after 7 months on diets containing as high as 350 ppm fluoride (as sodium fluoride), although postnatal mortality of kits maintained on the high-dose fluoride diet was increased. In contrast, decreased calving rates have been report in young cows given drinking water containing 5 mg/L fluoride for 4 years (Van Rensberg and De Vos, 1966), and poor growth, abnormal skeletal morphology and dental fluorosis have been observed in the offspring of cows receiving feed contaminated with fluoride (Maylin et al., 1987).

Early studies provided somewhat conflicting evidence for the possibility that fluoride is an essential element for normal fertility. It has been suggested that fluoride promotes a more efficient dietary utilization of iron and other trace minerals (Messer et al., 1973; Tao and Suttie, 1976). Further reports of avian and bovine studies have provided

evidence consistent with the concept that fertility impairment occurs when the animals are exposed to levels either higher or lower than normally occur in the diet (Guenter and Han, 1986; Carriere e al., 1987; Hoffman, 1985; Patee, 1988; Van Rensburg and De Vos, 1966). Inhibition of lactation in cows (Maylin and Krook, 1982) and silver foxes (Eckerlin et al, 1986) was observed after exposure to high levels of fluoride.

_Pages 66-67 DHHS, 1991.