Seveso Women's Health Study: A Study of the Effects of TCDD on Reproductive Health

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Introduction

The compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), is a pervasive by-product of industrial activities, including waste incineration. There is substantial animal evidence suggesting TCDD has developmental and reproductive effects. Birth outcomes associated with maternal TCDD exposure in animal studies include increased fetal mortality (1-5), increased fetal resorptions (3,4), decreased litter size (6), and reduced body weight of offspring (2,4,6,7). Effects of TCDD exposure on sexual maturation, fertility and fecundity, and estrus have also been noted including delayed onset of puberty and early onset of menopause (8,9), reduced ovulation rates and alterations in menstruation (10-12), decreased estradiol and progesterone levels (12,13), reduced fertility and fecundity (3,6,9,12,14), and increased incidence/severity of endometriosis (15). These articles, and other reports concerning profound reproductive effects, have led the U.S. Environmental Protection Agency (EPA) to argue that the non-cancer effects of this chemical may be a more urgent threat to humans than the potential cancer effects (16). Despite the extensive animal evidence of the adverse effects of TCDD exposure on reproduction, there is a paucity of information in humans.

In 1976, a chemical plant explosion in Seveso, Italy exposed the residents in the surrounding community to the highest exposure to TCDD known in humans (17). Materials from an aerosol cloud of sodium hydroxide, sodium trichlorophenate and TCDD were deposited over a 2.8 km^2 area (17). Initially, the contaminated area was divided into three major Zones (A, B, R) based on the concentration of TCDD in surface soils. Zone A, the most heavily contaminated area, sustained an immediate 25% animal mortality rate; however, residents of Zone A (n=735) were not evacuated until twenty days after the accident. The residents of Zone B (n=4,699), the area of next greatest contamination, were not evacuated but were warned about the risk of consumption of locally-grown food products. Zone R had 31,800 residents who were neither evacuated nor warned (17). As evidence of the significant level of TCDD exposure, 193 cases of chloracne were reported among residents of the area (18).

Initial reproductive studies in Seveso used zone of residence as a proxy measure of exposure and reported no change in birthweight or duration of pregnancy between 1975 and 1981 (19), increased rate of spontaneous abortions from 1976 to 1978 (20), no increase in birth defects from 1977 to 1982 (21), increased frequency of aberrant cells in cytogenetic analysis of aborted fetuses (22), and unusual ultrastructural appearance of placental morphology after induced abortion in 1976 (23). Preliminary serum TCDD data, however, suggest zone is not a good proxy measure of individual exposure. For 296 male and female residents of Zone A, TCDD measured in sera collected in 1976 ranged from not detectable to 56,000 ppt (personal communcation, Needham, 1997).)

In the first reproductive study in Seveso that used serum TCDD to measure exposure, a significant excess of female births (sex ratio =0.54) was found in Zone A from 1977 to 1984 (24). Preliminary results suggest high serum TCDD levels in both parents is associated with an excess of female births.

The Seveso cohort represents the largest population of TCDD-exposed women and the highest exposure known in humans (25). The relatively pure exposure to TCDD and the ability to quantify individual level TCDD exposure from sera collected in 1976 for the Seveso cohort affords a unique opportunity to evaluate the potential dose-response relationship between TCDD exposure and a spectrum of reproductive endpoints.

Material and Methods

The Seveso Women's Health Study (SWHS) is the first comprehensive epidemiologic study of the reproductive health of a female population exposed to TCDD. The primary objectives of the SWHS are to investigate the relationship of TCDD and the following reproductive endpoints: (1) endometriosis; (2) menstrual cycle characteristics; (3) age of menarche; (4) birth outcomes including rate of spontaneous abortion and birthweight of pregnancies conceived after 1976; (5) time to conception and clinical infertility; and (6) age of menopause. Included in the SWHS cohort are women 0 to 30 years old (Phase I) or 31-40 (Phase II) in 1976, who have adequate stored sera collected between 1976 and 1980, and who resided in the most heavily exposed areas, Zones A (n=234) or B (n=1,039) at the time of the

accident in 1976. Each woman is interviewed extensively about her reproductive and pregnancy history; has a blood draw, pelvic exam and transvaginal ultrasound; and is asked to complete a menstrual diary. Individual level TCDD exposure will be measured in sera collected between 1976 and 1980.

Results and Discussion

Enrollment for the Seveso Women's Health Study began in March 1996. More than 95% of the women were located twenty years after the accident and to date roughly 80% of the cohort have participated. We expect to complete all data collection in June 1998. Reports examining the first reproductive endpoint, endometriosis, will be completed by the end of 1998, other outcomes will be examined in subsequent years. Preliminary descriptive statistics will be presented.

In conclusion, there is substantial animal evidence suggesting that TCDD has developmental and reproductive effects. Previous human studies either include small numbers of women or no measure of individual exposure. The Seveso Women's Health Study is the first comprehensive reproductive health study of a TCDD-exposed cohort. Exposure will be assessed by TCDD in serum collected between 1976 and 1980.

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