Neurocognitive and physical functioning in the Seveso Women’s Health Study

Jennifer Ames\(^a\), Marcella Warner\(^a\), Paolo Brambilla\(^b\), Paolo Mocarelli\(^b\), William A. Satarianoc, Brenda Eskenazi\(^a,⁎\)

\(^a\) Center for Environmental Research & Children’s Health (CERCH), School of Public Health, University of California, Berkeley, CA, USA
\(^b\) Department of Laboratory Medicine, University of Milano-Bicocca, School of Medicine, Hospital of Desio, Desio-Milano, Italy
\(^c\) School of Public Health, University of California, Berkeley, CA, USA

**ARTICLE INFO**

**Keywords:**
Dioxin
Neurocognition
Endocrine disruptors
Women
Seveso

**ABSTRACT**

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is neurotoxic in animals but few studies have investigated its effects on the human brain. Related dioxin-like compounds have been linked to poorer cognitive and motor function in older adults, with effects more pronounced in women, perhaps due to the loss of neuro-protective estrogen in menopause. On 10 July 1976, a chemical explosion in Seveso, Italy, resulted in one of the highest known residential exposures to TCDD. In 1996, we initiated the Seveso Women’s Health Study, a retrospective cohort study of the health of the women who were newborn to 40 years old in 1976. Here, we investigate whether TCDD exposure is associated with physical functioning and working memory more than 20 years later. Individual TCDD concentration (ppt) was measured in archived serum collected soon after the explosion. In 1996 and 2008, we measured physical functioning (n=154) and working memory (n=459), respectively. We examined associations between serum TCDD and motor and cognitive outcomes with multivariate linear regression and semi-parametric estimators. A 10-fold increase in serum TCDD was not associated with walking speed (adjusted \(β=0.0006 \text{ ft/s}, 95\% \text{ Confidence Interval (CI): −0.13, 0.13}\), upper body mobility (adjusted \(β=−0.06, 95\% \text{ CI: −0.36, 0.23}\)), or manual dexterity (adjusted \(β=0.34, 95\% \text{ CI: −0.65, 1.33}\)). We observed an inverted U-shaped association in grip strength, with poorer strength in the lowest and highest TCDD exposure levels. There was no association between TCDD and the Wechsler digit and spatial span tests. Neither menopause status at assessment nor developmental timing of exposure modified associations between TCDD and working memory. Our findings, in one of the only studies of TCDD’s effects on neuropsychological and physical functioning in women, do not indicate an adverse effect on these domains, with the exception of a U-shaped relationship with grip strength. Given the limited assessment and relative youth of the women at this follow-up, future work examining additional neuropsychological outcomes is warranted.

**1. Introduction**

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a global environmental pollutant released into the environment through industrial sources of combustion. Due to its exceptional toxicological potency and chemical stability, TCDD ranks among the 2001 Stockholm Convention’s “dirty dozen” of ubiquitous persistent organic pollutants (POPs) (Lallas, 2001). TCDD exerts its biological toxicity primarily through its binding affinity for the aryl hydrocarbon receptor (AhR), a nuclear receptor and transcription factor that regulates myriad biological processes related to development, cell growth, apoptosis, and immune function (Denison et al., 2011). TCDD is a member of a wider class of halogenated aromatic compounds such as polychlorinated dibenzo-para-dioxins (PCDDs), dibenzo furans (PCDFs), and certain polychlorinated biphenyls (PCBs) that share this mechanism of action via the AhR. Dioxins bioaccumulate in adipose tissue (Kahn et al., 1988) and have a long half-life of 4–11 years in the human body (Milbrath et al., 2009; Warner et al., 2014). While levels of dioxins found in humans have decreased substantially over the last few decades, aging populations with high fish and meat consumption are particularly vulnerable to accruing higher, potentially toxic body burdens over the life course (LaKind et al., 2009).

*In vitro* studies demonstrate that TCDD-induced activation of the AhR, through altering endocrine function and expression of genes related to apoptosis and oxidative stress, promotes premature cell senescence in rat and human neurons and animal studies have reported...
impairments in memory, spatial and visual learning, and fear response with developmental exposure to TCDD and dioxin-like compounds (Curran et al., 2011; Hajima et al., 2010; Hojo et al., 2008; Schantz and Bowman, 1989; Schantz and Widholm, 2001; Seegal, 2000; Wan et al., 2014). However, few studies have investigated the neurotoxic effects of TCDD in humans. Studies of U.S. veterans exposed to TCDD through the spraying of Agent Orange during the Vietnam War have found that men with the highest dioxin exposures performed poorly on tests of motor coordination and verbal memory compared to their unexposed peers (Barrett et al., 2001; Wolfe et al., 1992). Neuropathic signs, writer’s dystonia, and tremor have also been documented in small studies of individuals exposed to TCDD occupationally and during the Seveso accident (Barbieri et al., 1988; Klawans, 1987; Singer et al., 1982; Urban et al., 2007). Several studies in general populations with exposures closer to background levels have found associations between dioxin-like PCB body burdens and impairments in motor function, memory, learning, and executive function (Fitzgerald et al., 2008; Haase et al., 2009; Peper et al., 1993; Schantz et al., 2001).

Susceptibility to the neurotoxic effects of dioxin may vary by sex and age. For example, an inverse association was observed between blood PCB concentrations and performance on tests of attention, visual memory, and learning ability among older Taiwanese women but not among men who were exposed as adults in 1979 to high levels of PCBs and dioxin-like compounds in contaminated cooking oil (the Yucheng cohort) (Lin et al., 2008). Similarly, a study of older adults in NHANES, where exposures were closer to background, found adverse associations between dioxin-like PCB serum concentrations and poorer cognitive scores, with the association most pronounced among women aged 70 + years (Bouchard et al., 2014). An excess of Parkinson’s disease, dementia, and amyotrophic lateral sclerosis was also observed among women occupationally exposed to PCBs (Steinland et al., 2006). Given the wide cross-talk of the AhR with several hormonal pathways, the mechanism underlying these interactions between age, sex, and exposure to dioxin-like compounds may be exacerbated by the loss of estrogen’s neuroprotective effects during and after menopause (Koyama et al., 2016). Estrogen-related loss of brain dopamine could also contribute to lowered physical functioning and reductions in muscle mass and strength following menopause (Sowers et al., 2007).

In the present study, we investigated the neurotoxic effects of dioxin in the Seveso Women’s Health Study (SWHS), a historical cohort study of women residing around Seveso, Italy at the time of an industrial accident on July 10, 1976 that resulted in one of the highest levels of residential TCDD contamination known (Mocarelli et al., 1988). We hypothesized that higher 1976 serum concentrations of dioxin would be inversely associated with physical and cognitive functioning and that adverse associations would be most pronounced in postmenopausal women. In addition to susceptibility factors at the time of assessment, we also considered differences in susceptibility among those exposed at younger ages, while the brain, particularly areas related to working memory such as the prefrontal cortex, are still developing (White and Swartzwelder, 2005). The study of neurodevelopmental effects of dioxin have largely focused on the perinatal period but the continued susceptibility of the brain to environmental toxicants during its rapid growth, neuronal pruning, and maturation during childhood and young adulthood (up to about 25 years of age) is not well understood (Golub, 2000; Weiss, 2013).

2. Methods

2.1. Study population

Recruitment of the SWHS cohort has been described previously (Eskanazi et al., 2000). Briefly, this historical cohort study recruited eligible women who were newborn to 40 years of age on July 10, 1976, resided at that time in the highest contaminated areas (Zones A and B), and had adequate stored serum for analysis of TCDD collected soon after the explosion. Enrollment took place from March 1996 to July 1998, and 981 women (80% of those eligible) participated. The oldest women (31–40 years in 1976) who were interviewed after September 1997 (n = 173 of 229) were invited to participate in an assessment of physical functioning added as part of the study visit. Of those invited, 19 women refused to participate in any of the tests leaving 154 women (89% of eligible) who completed the physical function tests.

Between April 2008 and December 2009, we conducted a follow-up of the SWHS cohort: 833 (85%) of the original 981 women could be contacted and participated (16 were deceased and 36 could not be located). Data collection was already underway when findings of lowered working memory and other neuropsychological measures in the Yucheng cohort were published (Lin et al., 2008). This motivated development of an ad-hoc assessment of neuropsychological outcomes in the SWHS. Starting in December 2008, partway through the 2008–2009 follow-up of the cohort, remaining participants (n = 459) were invited to complete an assessment of working memory as part of the study visit. We excluded two with Turner’s syndrome leaving 457 participants.

2.2. Procedure

The study was approved by the Institutional Review Boards of the participating institutions and written informed consent was obtained from all women prior to participation. Details of the study procedure for the 1996 and 2008 studies are described elsewhere (Eskanazi et al., 2000; Warner et al., 2011). In both 1996 and 2008, information on covariates such as demographic and lifestyle factors and medical history were obtained from a questionnaire administered in private by a trained nurse-interviewer and followed by a brief medical exam which included anthropometric and blood pressure measurements. Interviewers were blinded to participants’ serum TCDD levels and zones of residence.

2.3. Laboratory analyses

Archived serum samples collected in 1976 were stored at −20 °C until shipped to the Centers for Disease Control and Prevention (CDC) for analysis in 1998. TCDD was measured in archived sera by high-resolution gas chromatography/high-resolution mass spectrometry methods (Patterson et al., 1987). Prior to statistical analysis, serum TCDD levels were adjusted for blood lipid concentrations by dividing TCDD on a whole-weight basis by total serum lipid content, estimated from measurements of triglycerides and total cholesterol (Akins et al., 1989). Serum TCDD levels were reported in picograms per gram lipid or parts per trillion (ppt). The median serum sample weight for these samples was 0.65 g, and the median lipid-adjusted limit of detection was 18.8 ppt. Samples below the limit of detection (LOD) (9.4% in full cohort) were assigned a value equal to one-half of the LOD (Hornung and Reed, 1990). Details of the serum sample selection and TCDD concentrations measured in 1976 serum are presented elsewhere (Eskanazi et al., 2000, 2004).

2.4. Physical function assessment in 1996

The physical function assessment administered in 1996 included four validated physical tasks chosen for their ease of implementation, reliability, and frequent use in studies of community-dwelling older adults (Tager et al., 1998): 1) a 10-foot walking test of functional mobility, 2) a coin-flipping test of manual dexterity, 3) a grip strength test, and 4) a reach down test of lower body mobility (Muriel Lezak et al., 2012). Together, these tests represented a diverse cross-section of physical performance. For the 10-foot walking test, participants were asked to walk back and forth on a 10-foot long course for two minutes at their regular speed as if walking down the street to go to the store. We used the number of lengths walked in this time to calculate the average walking speed (ft/s). For the coin flip test, participants were
دریافت فوری متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات