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Association of dioxin exposure and reproductive hormone levels in men living near the Bien Hoa airbase, Vietnam

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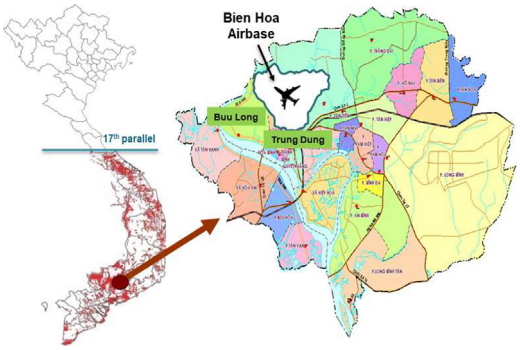
HIGHLIGHTS

- We studied the effects of dioxin on reproductive hormone levels in Vietnamese men.
- Dioxin and total testosterone levels were negatively correlated.
- Dioxin and prolactin levels were positively correlated.
- Future studies should assess dioxins' effects on the endocrine system as a whole.

GRAPHICAL ABSTRACT



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ABSTRACT

Dioxins are endocrine-disrupting chemicals, and their effects on reproductive functions are well-documented. The aim of the present study was to measure the levels of reproductive hormones in 42 men residing near a dioxin-contaminated area in Vietnam. We measured levels of 17 2,3,7,8-substituted congeners of polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) and four non-ortho polychlorinated biphenyls (PCBs) in blood. Levels of follicle-stimulating hormone, luteinizing hormone, progesterone, prolactin, estradiol, and total testosterone were measured in serum. Blood dioxin levels were elevated; the levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin was 7.3 pg/g fat. Seven of the men had testosterone levels below 250 ng/dL, and nine men had prolactin levels above 9.7 ng/mL. Four PCDD congeners, two PCDF congeners, one PCB congener, and the sum TEQ of PCDDs, PCDDs/Fs, and PCDDs/Fs/PCBs were positively and significantly correlated with prolactin levels. Two PCDD congeners, six PCDF congeners, two PCB congeners, and the TEQs of PCDFs and PCBs were negatively and significantly correlated with testosterone levels. There were no significant correlations between dioxin congeners and follicle-stimulating hormone, luteinizing hormone, or progesterone levels.

Abbreviations: 2,3,7,8-TetraCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; PCDDs, polychlorinated dibenzo-p-dioxins; PCDFs, polychlorinated dibenzofurans; PCBs, polychlorinated biphenyls; TEQ, toxic equivalent; GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

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1. Introduction

Dioxin from herbicides used during the Vietnam war is an ongoing public health concern. More than four decades after the war ended, former U.S. airbases in Da Nang, Phu Cat, and Bien Hoa are still a hotspot of dioxin contamination (Hatfield Consultants, 2007, 2011). The contamination is attributable to the storage, loading, spillage, and handling of herbicides, mostly Agent Orange, during Operation Ranch Hand (1962–1971) in Southern Vietnam (Stellman et al., 2003). Populations around these airbases have a high risk of ingesting dioxin from water and contaminated harvests (Schecter et al., 2003). Dioxin levels in breast milk of mothers living near the Da Nang and Bien Hoa airbases have been correlated with the length of time the women resided in the area, suggesting that dioxin exposure was still a concern (Nghi et al., 2015; Tai et al., 2011).

Populations in these dioxin-contaminated areas are at risk of adverse health effects. In our previous work, we showed that perinatal dioxin exposure around the Da Nang airbase affected infant neurodevelopment and physical development; exposure to high levels of dioxin decreased cognitive, expressive communication, and fine motor skills in 4-month-old infants, as well as socialization skills in toddlers aged 1 and 3 years (Nishijo et al., 2014; Tai et al., 2013, 2015, 2016). Exposure also decreased parameters of body size in males and increased abdominal and head circumference in females during the first three years of life (Nishijo et al., 2012; Tai et al., 2016). In addition, our studies of populations living near the Phu Cat airbase have suggested that dioxin influences steroidogenesis in humans (Kido et al., 2014; Manh et al., 2013; Sun et al., 2014).

Dioxins and polychlorinated biphenyls (PCBs) are known endocrine disruptors, and the effects of dioxin on reproductive functions in laboratory animals are well-documented. In rats, dioxin inhibits the secretion of luteinizing hormone (LH) and the response of the pituitary gland to gonadotropin-releasing hormone secreted by the hypothalamus (Bookstaff et al., 1990a; Moore et al., 1989), as well as decreasing total plasma testosterone (Moore et al., 1985). Numerous adverse reproductive and developmental effects have been noted in male laboratory animals exposed to dioxin, including reduced testicular weight, impaired spermatogenesis, decreased testicular secretion, testicular hypoplasia, and atrophy of the androgen-sensitive seminal vesicles and epididymis (Bookstaff et al., 1990b). In humans, accidental or high occupational exposure to these chemicals during manufacturing processes has been associated with reproductive functions. In the U.S. Air Force Health Study of Ranch Hand veterans who participated in the aerial spraying of Agent Orange in Vietnam, serum dioxin levels were significantly correlated with decreased testicular size, and trended to decreased serum testosterone levels (Roegner et al., 1991; Gupta et al., 2006). Egeland et al. (1994) found an inverse association between serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TetraCDD) and serum testosterone levels in chemical production workers. Men prenatally exposed to PCBs and polychlorinated dibenzofurans (PCDFs) during the Yucheng rice oil poisoning incident had a higher percentage of sperm with abnormal morphology and lower sperm motility (Guo et al., 2000). In the Seveso disaster of 1976, exposure to 2,3,7,8-TetraCDD in infancy reduced sperm concentration and motility, while an opposite effect was observed in males exposed during puberty. Exposure in either period leads to permanent reduction of estradiol and increased follicle-stimulating hormone (FSH), along with a reduction in the concentration of LH in groups exposed during puberty (Mocarelli et al., 2008).

Only a few studies have been conducted to date on the health effects of dioxin in the population living around the Bien Hoa airbase, even though it is considered the largest and most dioxin-contaminated area in Vietnam (Hatfield Consultants, 2011). The aim of this study was therefore to investigate the association between dioxin exposure and reproductive hormone levels in men living around the Bien Hoa airbase.

2. Materials and methods

2.1. Study sites and subjects

The Trung Dung and Buu Long communes in Bien Hoa City, located in close proximity to the Bien Hoa airbase, were selected as the study sites. Residents of these communes were considered highly exposed (Nghi et al., 2015). A total of 42 men were recruited for the study in 2014. To be enrolled, men had to have resided >15 years in the area, be 20–50 years old, and to have received no hormone therapy or hormone-disrupting medications within one month prior to enrollment.

Written informed consent was obtained from all subjects according to a process reviewed and approved by the Health Department of Bien Hoa City. The institutional ethics board of Vietnam Military Medical University approved the study design. Demographic information for each subject, including age, length of residency, education, employment, smoking status, and alcohol consumption, were collected by interview.

2.2. Determination of dioxin levels in blood

Twenty milliliters of venous blood were collected from each subject in the morning after an overnight fast. The whole-blood samples were frozen at −80 °C until analysis. Blood samples were freeze-dried (Eyela FDU-1200, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) for 8 h. Next, the samples were manually milled into fine powder. Fat was extracted by using an accelerated solvent extraction system (ASE 200, Thermo Fisher Scientific, Waltham, MA, USA) with 1:1 hexane and acetone. Blood lipid contents were determined by a highly accurate scale before ^{13}C-labeled 2,3,7,8-substituted PCDDs/Fs (DF-LCS-A40, Wellington Laboratories Inc., Guelph, ON, Canada) and non-ortho PCBs (EC-5324, Cambridge Isotope Laboratories, Inc., Tewksbury, MA, USA) were added as internal standards. Purification processes, including alkali digestion, hexane extraction, and chromatography on a multilayered silica gel column, were performed. A single-layered column of activated carbon dispersed on silica gel was used to separate and collect dioxin and PCB fractions. In total, the levels of 17 2,3,7,8-substituted congeners of polychlorinated dibenzo-p-dioxins (PCDDs) and PCDFs and four non-ortho PCBs were determined by high-resolution gas chromatography/mass spectrometry (HRGC/MS, MStation-JMS700, JEOL, Tokyo, Japan) at Kanazawa Medical University, Japan. If concentrations were lower than the limit of detection, congeners were assigned a value half of those limits. The established method of analysis has been described in detail elsewhere (Tawara et al., 2003). Levels of individual congeners were recorded as pg/g fat. The cumulative toxic equivalent (TEQ) values of PCDDs, PCDFs, PCDDs/Fs, PCBs, and PCDDs/Fs/PCBs were determined by summing up the TEQs of each dioxin congener referenced in the World Health Organization 2005 TEQ factor list (Van den Berg et al., 2006).

2.3. Determination of reproductive hormone levels in serum

Blood samples for hormone measurements were collected between 8:00 and 10:00 in the morning after an overnight fast. Serum was separated and stored at −80 °C until analysis. Levels of FSH, LH, progesterone, prolactin, estradiol, and total testosterone were measured using an IMMULITE® 2000 XPi analyzer (Siemens, Munich, Germany) in the analytical laboratory of Vietnam Military Medical University. Quality control protocols were applied with strict criteria for all tests. Reference ranges of reproductive hormones in the analytical laboratory were set as follows: FSH, 1.5–10 mIU/mL; LH, 1.8–8.6 mIU/mL; progesterone, 0.1–1 ng/mL; prolactin, 1.5–9.7 ng/mL; estradiol, 10–60 ng/mL; total testosterone, 250–1100 ng/dL. Low, medium, and high levels of each hormone were defined as lower than the reference range, within the reference range, and higher than the reference range, respectively.