Dioxins, Male Pubertal Development, and Testis Function

Project Scope

While there is substantial evidence that chlorinated dibenzodioxins (dioxins) are potent developmental and reproductive toxins in animal systems, there is little data available concerning that adverse effects of early exposures to these chemicals in human populations. Specific concern centers on whether exposure to dioxins and related compounds causes altered growth and sexual maturation in boys. Human exposures to dioxins are generally low in North America, but industrial activity has resulted in areas of significant contamination elsewhere in the world. This grant is supporting research that is monitoring the growth patterns, sexual maturation, and reproductive hormone levels in a group of Russian boys exposed to dioxins by virtue of living near a heavily contaminated industrial site.

The specific objectives of the project are to: (1) investigate the relationship between exposure to dioxins (and dioxin-like compounds) and somatic (non-reproductive cell) growth, weight gain, and body mass index in the target population; (2) explore the relationship between serum levels of dioxins and dioxin-like compounds and the timing and rate of pubertal development; and (3) investigate the biological processes underlying the effects of dioxins and dioxin-like compounds on growth and pubertal maturation.

This research, which is still in progress, is a prospective cohort study designed to determine the association between dioxin exposures and physical growth and the timing of pubertal development in boys living in(though not necessarily born in) Chapaevsk, Russia. The subjects have experienced documented high exposures to dioxins from a large chemical-industrial complex built during World War II to manufacture chlorine-containing compounds, including chemical warfare agents. The study protocol called for the recruitment of a cohort of approximately 500 boys ages 8 and 9 years between March 2003 and April 2005. At recruitment, baseline examinations are focusing on physical and physiologic markers of growth and pubertal development. Blood samples are being collected and analyzed for dioxins. Health, lifestyle, and diet information also is being collected. Yearly physical exams will assess growth velocity and onset and tempo of sexual maturation. Statistical modeling will be used to explore the relationship between serum levels of dioxin and altered physical growth and sexual maturation.

Grant Title and Principal Investigator

Dioxins, Male Pubertal Development and Testis Function

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Key Findings

- This grant is funding a study of potential growth and reproductive impacts of dioxin exposure in a cohort of 8-9 year-old Russian boys exposed to dioxins from a chemical plant. A previous pilot study indicated that in the town of Chapaevsk, where a documented high exposure to dioxins exist due to a chemical-industrial complex, boys are thinner than both U.S. and Russian boys in general, and Chapaevsk boys have a later onset of puberty and attainment of sexual maturity than boys from other countries.
- In further analysis under this grant of a subset of the pilot study cohort, older age and consumption of local meats and fish were found to be predictors of the sum of dioxins in the boys' serum. There also was a suggestive, though non-significant, inverse association between current residential distance to the chemical plant and total dioxin levels in blood samples. There was no difference in dioxin levels between the groups of boys with congenital abnormalities and the control boys (though the small size of the study limits its power to detect differences).
- The main study being funded under this grant will monitor the growth, sexual maturation, and reproductive hormone levels in 500 8- and 9-year old Chapaevsk boys, and characterize adverse effects associated with dioxin exposures.

Research partially or fully under this grant has been the subject of three peer-reviewed articles.

Project Results

In a pilot study conducted from 1998 to 2000 (prior to this particular STAR grant funding) the investigators characterized the physical growth and sexual maturation in 2,579 boys, ages 10 through 16.99 years residing in Chapaevsk in order to establish region-specific reference data. Age specific norms were established for anthropometric factors such as height, weight, and basal metabolic index (BMI) and compared to U.S. reference data by z-score analysis, while mean heights and weights by age were compared to published national Russian data. This study led researchers to conclude that Chapaevsk boys are thinner than both U.S. and Russian boys, and have a later onset of puberty and attainment of sexual maturity than boys from other countries.

Under the current STAR grant, pilot data are being analyzed to both guide the optimal design of the prospective cohort study of 8 and 9-year old boys and to provide normative data for the boys in this community of Russia. A subset of the boys evaluated in the pilot study was selected for blood sampling and historical questionnaires. Thirty of the blood samples were then analyzed for dioxins, furans, and PCBs and a statistical analysis was performed to determine predictors of serum dioxin levels. Fifteen of the samples were from boys with congenital genitourinary abnormalities and the other fifteen were from "control" boys without congenital abnormalities. The questionnaire collected information about diet, medical history, lifestyle, and residential distance from the chemical-industrial plant (the main source of the environmental dioxins in Chapaevsk; see Figure 1). The results of the statistical analysis indicated that greater age and consumption of locally grown meats and fish (i.e., grown/obtained in Chapaevsk) were predictors of the dioxin levels in the boys' serum. There was a suggestive, though non-significant, inverse association between current residential distance to the chemical plant and sum of dioxin congeners measured in the blood samples. There was no difference in dioxin levels between the groups of boys with congenital abnormalities and the control boys. However, the small size of the study only limited its sensitivity. The results of this study helped guide the exposure assessment design for the main cohort study

As of February 2005, approximately 450 families had been recruited to participate in the study. Each of the study subjects and their mothers provided a blood and urine sample, and their questionnaire responses were entered into a database containing over a thousand variables. Baseline measurements focused on physical and physiological markers of pubertal development. Physical markers include measurement of anthropometric factors and determination of secondary sexual characteristics and gonadal maturation assessed by Tanner staging for genital and pubic hair development and measurement of testicular volume. Physiological markers consist of biochemical measures assessed by increased levels of reproductive hormones, such as follicle-stimulating hormone, luteinizing hormone, testosterone, prolactin, inhibin-B, and mullerian-inhibiting substance. Researchers will follow the boys yearly until age 18 when reproductive fitness can be assessed by collecting a semen sample.

Relevance to ORD's Multi-Year Research Plan

This project contributes to the first two of ORD's Multi-Year Plan long-term goals (LTGs 1 and 2): (1) providing a better understanding of the science underlying the effects, exposure, assessment, and management of endocrine disruptors and (2) determining the extent of the impact of endocrine disruptors on humans. Specifically, this research is helping to characterize the effects of exposure to multiple endocrine disruptors (mixed dioxins) in young boys; characterize the critical biological factors during development that may be associated with adverse reproductive outcomes later in life; determine the extent to which exposure to endocrine disruptors contribute to the onset or increase in the severity of diseases; evaluate exposure methods, measurement protocols, and models; determine whether adverse developmental and reproductive effects are occurring in human populations following exposure to endocrine disruptors; and determine sources of exposure and environmental fates of endocrine disruptors.

Investigators

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NCER Project Abstract and Reports
http://cfpub2.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/2360/report/0

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