A CASE-COHORT STUDY OF CRYPTORCHIDISM, HYPOSPADIAS AND DELAYED SEXUAL MATURATION IN A DIOXIN CONTAMINATED REGION: CHAPAEVSK, RUSSIA

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Introduction

Chapaevsk, Russia with a population of 83,000, is located 43 km southwest of Samara, on the Chapaevka River, which flows into the Volga River. The city occupies an area of 187 km^2, half of which is occupied by industries that are mostly of the military-industrial complex. One of the largest environmental polluters in Chapaevsk is the Middle Volga Chemical (SVZH, Himprom) plant, which produced hexachlorocyclohexane (lindane) and its derivatives from 1967 to 1987. Since then, the plant has produced agricultural pesticides containing chlorine. Byproducts of the manufacturing process include dioxins and furans, which contaminated the region. For example, high dioxin levels in soil (141 ng TEQ/kg less than 2 km from plant), drinking water (12.3 pg TEQ/L), and cow's milk (17-61 pg TEQ/g fat) have been found in samples from Chapaevsk.[1] The average dioxin level in blood samples collected in 1998 from six Chapaevsk residents living within 3 kilometers of the plant was 75 pg/TEQ/g lipid[1], two to three fold higher than levels reported among general population samples in the U.S.[2]

Cryptorchidism (undescended testicles) and hypospadias are common minor congenital anomalies of male reproductive tract development [3]. Although several risk factors have been identified, the etiology of both disorders remains largely unknown. Recently, the possibility that these minor reproductive tract abnormalities may be related to exposure to environmental contaminants, such as the hormonally active dioxins, has been raised.[4, 5] Therefore, we designed a study to investigate the potential association of dioxin exposure to cryptorchidism, hypospadias, and delayed sexual maturation in adolescent aged boys living in Chapaevsk, Russia.[6] The current analysis is a description of the study population with emphasis on residential proximity to Himprom and other potential risk factors for dioxin exposure among Chapaevsk residents.

Methods and Materials

The first phase of the study, conducted from March to May 1999, consisted of a survey of 10-16 year old boys in Chapaevsk[7]. Participants that agreed to participate underwent a physical examination, with particular attention to the presence of cryptorchidism and hypospadias, and the pubertal stage of

maturation. Among 3041 age-eligible boys identified via birth and school records, 2580 (84.8%) boys were enrolled.

Physical examinations of the children were performed by a pediatric endocrinologist and an urologist. Pubertal maturation was graded according to Tanner Staging for genitalia[8] and pubic hair with testicular volume determined using an orchidometer (Prader beads). Testicular location and the presence of typical orchidopexy postoperative scars were noted. The presence of hypospadias was based on the location of the external urethral meatus. The childrens' birth records were reviewed to identify additional cases of cryptorchidism and hypospadias. Delayed sexual maturation was defined as boys who had not attained stage 2 pubarche by the age of 14 years, stage 3 by age 15, or stage 4 by age 16. In addition, boys with testicular volumes considered small for age (<4 cc for age>13.5 years, <8 cc for age>14.5 years, <10 cc for age>15.5 years, or <12 cc for age>16.5 years) and those with stretched penile length in the 1st percentile (age<13.5 years) or 3rd percentile (age>13.5 years) were identified and included in the category of delayed maturation.

The second phase of the study, conducted from October 1999 through May 2000, focused on a subset of 112 boys (14-16 years old) from phase one identified by the presence or absence of cryptorchidism, hypospadias, and delayed puberty, along with 134 controls chosen using a case-cohort design. The number of targeted control boys was proportionate to the average of the percentage of cases and overall percentage of boys within each of the three age strata. These 246 children were targeted for a more thorough assessment, including blood and urine samples for organochlorine contaminant and hormone measurements, and administration of a detailed questionnaire on medical history, diet, and lifestyle. Among the 246 children, 221 (90 %) mother-child pairs agreed to participate and 208 (85 %) of these completed the questionnaire. Blood samples collected from 200 mothers (81 %) and 220 children (89 %) were archived for later determination of dioxins, furans and PCBs, as well as for metals (lead).

We generated maps of the distribution of participants' residence location relative to the Himprom factory. The electronic map of Chapaevsk was constructed with the use of a geographic map of scale 1:10000 and ArcView GIS 3.0. The dots on the map approximate the residential addresses of the boys and were placed using a geocoding process.

Results and Discussion

The residential distribution of the 2580 boys recruited into the first phase of the study is shown in Figure 1. Among the 2580 children examined in phase one, the residential distribution for the 45 cases of cryptorchidism (1,7 %), 16 cases of hypospadias (0,6 %) and 139 cases of delayed sexual development (5,4 %) is shown in Figure 2. A subject may be classified in more than one case category.

In phase two, information on the residential address of the mother during her pregnancy and the work history of both parents prior to and during the pregnancy was available in 95 cases and 113 controls. While pregnant with the index son, 24 % of mothers lived within two km of the Himprom factories, while 39 % lived two to six km from the factories, and 38 % lived more than six km from the factories (these do not add to 100 % due to rounding). Although 88 % of mothers worked during the year prior to becoming pregnant with the index son, only 4 % worked at the Himprom factories and most worked at other companies or at businesses outside Chapaevsk. To assess the children's consumption of foods that were locally grown (vegetables) or raised (cows, chickens, pigs), and therefore potentially contaminated with dioxins, the questionnaire collected a dietary history on the index son. Preliminary results showed that a high proportion of the boys consumed locally grown or raised foods during their lifetime: over 70 % consumed locally produced dairy products, over 50 % consumed locally raised chickens or eggs, and over 80 % consumed locally caught fish during their lifetime.

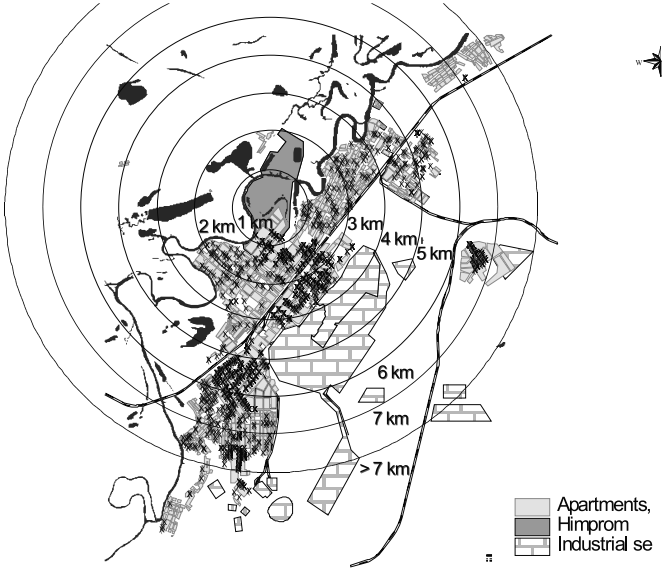

Figure 1. Distance from the Himprom factory for the 2580 boys enrolled into phase one of study.

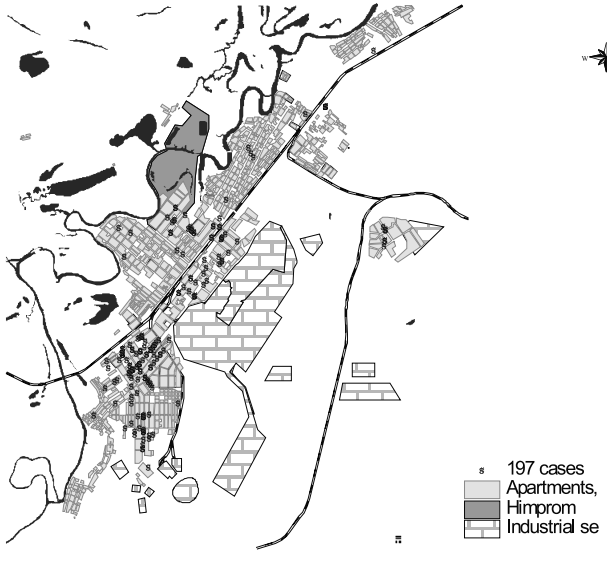

Figure 2. Distribution of the 197 cases identified in phase one of the study within the Chapaevsk area.

An exploratory analysis using the residential history and dietary history information as surrogates for dioxin exposure is currently in progress. Specifically, we are exploring whether these surrogates for dioxin exposure are associated with case-control status for cryptorchidism, hypospadias and/or delayed

sexual maturation. A portion of the phase two study blood samples are currently being analyzed for dioxins and furans and should be available by June 2002.

Acknowledgments

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