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The association of peripubertal serum concentrations of organochlorine chemicals and blood lead with growth and pubertal development in a longitudinal cohort of boys: A review of published results from the Russian Children's Study

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Abstract

Organochlorine chemicals and lead are environmental exposures that have endocrine disrupting properties (EDCs) which interfere with many aspects of hormone action. Childhood and adolescence are windows of susceptibility for adverse health effects of EDCs. Our ongoing study, the Russian Children's Study (RCS), is one of the few longitudinal studies investigating the impact of EDCs on growth and puberty in boys. It is conducted in the historically contaminated city of Chapaevsk, in the Samara region. The study focuses on evaluating the associations of persistent organochlorine chemicals and lead with growth and pubertal timing. At enrollment in 2003–2005, we collected blood from 516 boys at ages 8–9 years to measure dioxins, furans, polychlorinated biphenyls (PCBs), chlorinated pesticides and lead. At enrollment and at annual visits through age

18–19 years, a physician performed physical examinations that included pubertal staging and testicular volume measurements. We review the history of Chapaevsk as a research site and summarize published RCS data on the association of peripubertal serum concentrations of organochlorines and blood lead levels with growth, pubertal onset and sexual maturity. Overall, we found that persistent organochlorines and lead negatively affected growth during puberty. Our results also suggest that total toxic equivalents (TEQs), dioxin-like compounds, organochlorine pesticides and lead may delay, while nondioxin-like-PCBs may advance, the timing of male puberty. These findings promoted remediation programs in Chapaevsk, with improvement in health indicators, resulting in Chapaevsk being designated a member of the World Health Organization network “Healthy Cities” in 2015.

Keywords

puberty; dioxins; pesticides; PCBs; endocrine disrupting chemicals

Introduction

Endocrine disrupting chemicals (EDCs) are heterogeneous compounds with different properties that “interfere with any aspect of hormone action” (1, 2). Some EDCs, e.g., organochlorine compounds such as dioxins, polychlorinated biphenyls [PCBs], or organochlorine pesticides [OCPs]), and metals are persistent in the environment with long half-lives, whereas others (e.g. bisphenol A) are much shorter-lived (3). Developmental windows of susceptibility to EDCs include adolescence, a time of dramatic hormonal changes and growth (4, 5). However, few longitudinal studies have investigated associations of EDCs with growth and pubertal timing.

One such study is the Russian Children’s Study (RCS), a prospective cohort study that has focused on assessing the associations of persistent organochlorines and lead with male growth and pubertal timing. The RCS is conducted in Chapaevsk, Samara region, Russia, a city that was historically contaminated by industrial chemicals.

Chapaevsk and the inception of the RCS

Chapaevsk, a town of approximately 83,000 in 1959–1999 and 72,000 residents in 2002–2016, is located approximately 1000 kilometers southeast of Moscow (6, 7). Throughout the former USSR many chlorine production centers were built in towns such as Ufa, Dzerzhinsk and Chapaevsk (8). Beginning in 1915, chlorinated chemicals were produced at the Middle Volga Chemical Plant, i.e. SVZH, also known as Plant #102, Plant of Chemical Fertilizers, Volgopromkhim in Chapaevsk and referred to as Khimprom in our prior publications (6, 7, 9, 10). The plant produced chemical blister agents (mustard gas and lewisite) prior to 1949, then OCPs, such as derivatives of hexachlorocyclohexane, e.g. γ -hexachlorocyclohexane (lindane) and β -hexachlorocyclohexane (β HCH), hexachlorobenzene (HCB), pentachlorophenol, and polychlorocamphene (toxaphen) until 1987, and other chlorinated chemicals (liquid chlorine, perchloric acid, methyl chloroform, and vinyl chloride) until its closure (6). Manufacturing activity at the chemical plant started decreasing in 1991, and ceased in 2003. 4,916 workers (2,328 women) were employed at this chemical plant in 1984

and 2,063 workers (891 women) in 1997, approximately 10% and 4% of all Chapaevsk working-age adults (11, 12), respectively. Throughout its operation, dioxins were generated as by-products of the manufacturing process and waste incineration (8).

Beginning in 1994, ecological studies supported by the Chapaevsk local government were conducted to estimate levels of dioxins and OCPs in blood and breast milk, and to assess cancer and reproductive health risks among residents. Higher levels of these compounds were detected in local environmental and food samples, as well as in serum and breast milk samples from Chapaevsk residents compared with non-occupationally exposed populations in other parts of Russia, Europe, and the United States (6, 13, 14). The observed cancer mortality rate in Chapaevsk males was higher than the overall Samara region, especially for lung and urinary tract cancers, and infant and total mortality rates were also higher (6). Studies found decreased semen quality (15), and an increased rate of breast cancer in chemical plant workers and those who ate local pork or fish (16).

Throughout recent decades, research teams comprising more than 30 investigators from Russia and the United States conducted studies in Chapaevsk. The RCS began after an initial collaboration of researchers from Russia (Chapaevsk, Samara and Moscow) and the U.S. (Harvard T.H. Chan School of Public Health, Brigham and Women's Hospital, and Massachusetts General Hospital in Boston) on a cross-sectional pilot study of growth and pubertal development among 2,579 Chapaevsk boys who were 10–16 years old in 1998–1999 (17). We reported that Chapaevsk boys were thinner than boys from either the U.S. or other regions of Russia, and had a later onset of puberty and attainment of sexual maturity (17). Increased frequency of cryptorchidism, varicocele and delayed puberty was reported among these adolescents (18) and total serum toxic equivalents (TEQs) from a subset of 30 Chapaevsk boys were higher than that of other cohorts (19). Dietary consumption of local foods, as well as the boy's chronological and gestational age, were identified as important predictors of serum dioxin concentrations (19).

Russian Children's Study: design overview

The RCS is a prospective cohort of 516 8 to 9 year old boys who resided in Chapaevsk between 2003–2005 (10, 20, 21). After study enrollment, they were followed annually through 18 to 19 years of age. Enrollment rate was high, 90% of all eligible boys in Chapaevsk participated (21), and retention has remained high over the decade of follow-up (Figure 1). During each annual follow-up visit, physical examinations were performed with pubertal staging and testicular volume measurements. Cumulatively, more than 4500 visits have been conducted as of July 2016. Dr. Sergeyev established a Human Studies Institutional Review Board in Chapaevsk that reviewed and approved the study each year. The study was also approved annually by the Human Studies Institutional Review Boards of the Harvard T. H. Chan School of Public Health, University of Massachusetts Medical School, and Brigham and Women's Hospital. The parent or guardian provided informed consent and the boys signed assent forms. At age 18 years the young men signed informed consent forms. At study entry, each boy's parent or guardian completed nurse-administered health and lifestyle questionnaires (19) ascertaining birth and medical history, and demographic and socioeconomic status (SES) information. A validated Russian Institute of

Nutrition semi-quantitative food frequency questionnaire was administered by a research nurse for each child (22, 23).

Physical examination

At study entry and annual follow-up visits, a standardized anthropometric examination (24) was performed by a trained research nurse and pubertal staging was assessed by a single physician-investigator (OS). Age-adjusted z-scores were calculated for height (HT-*Z*) and BMI (BMI-*Z*) using the World Health Organization standards (25). Pubertal assessments were based on a 1–5 scale for genitalia and pubic hair staging by visual inspection (26), testicular volume (TV) was measured using Prader (Genentech, Inc., San Francisco, CA, USA) and Andrology Australia (27) orchidometers, and penile length was measured in centimeters with a wooden ruler. Indicators for pubertal onset were pubic hair (P) 2, genitalia (G) 2, or maximum TV > 3 mL. Indicators for sexual maturity were P5, G5, or TV ≥ 20 mL. TV has been reported to be the most robust, objective metric for pubertal stage assessment (28), therefore we will present only the results based on TV. Blood samples for chemical, hormonal, genetic and epigenetic analyses were collected at baseline and biennially, and urine samples annually.

Blood and serum sample analysis for exposure assessment

Organochlorine compounds (OCs) and lead were measured in entry visit serum and whole blood samples for 482 and 489 boys, respectively. Lead was analyzed by Zeeman background-corrected, flameless graphite furnace, atomic absorption spectrometry (ESA Laboratories, Chelmsford, MA; detection limit 1.0 µg/dL). OCs, including 7 dioxins, 10 furans, 41 PCBs, two pesticides (HCB and βHCH), and the dichlorodiphenyltrichlorethane metabolite *p,p'*-dichlorodiphenyl-dichloroethylene (*p,p'*-DDE) were quantified at the Centers for Disease Control and Prevention (CDC, Atlanta, GA) using selected-ion-monitoring (SIM) high resolution (10,000 resolving power) mass spectrometry (HRGC-ID/HRMS) (29). Values below the limit of detection (LOD) were assigned a value equal to the LOD divided by the square root of 2 (30). Total serum lipid content was determined from enzymatic measurements of total cholesterol and triglycerides (31). OCs were expressed as lipid-standardized concentrations (wet-weight concentrations divided by lipid concentrations), wet-weight concentrations, or as the lipid-standardized sum of the toxic-equivalency factor-weighted dioxin-like concentrations (TEQs). OCs were grouped into sums of dioxin-like compounds (ΣDLCs): polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like co-planar PCBs (C-PCBs); ΣTEQs (PCDDs, PCDFs, C-PCBs and mono-*ortho* PCBs [M-PCBs]); nondioxin-like PCBs (ΣNDL-PCBs, including M-PCBs); and OCPs.

Statistical analysis

We used mixed-effects regression models for repeated measures to assess the associations between the boys' baseline serum lipid-standardized sum of OC concentrations and blood lead levels (BLL) with longitudinal age-adjusted height and BMI z-scores and height velocity (HV), controlling for potential confounders (32, 33). OCs were categorized in quintiles to provide information on dose response patterns, and lead was dichotomized as high vs. low BLL (≥ 5 versus <5 µg/dL). In our early analyses, we assessed the associations

between quartiles of DLCs, TEQs, NDL-PCBs with pubertal onset among boys ages 8–12 years using multivariable Cox-proportional hazards models (21). Subsequently, among boys ages 8 to 17 or 18 years, we assessed associations between quartiles of DLCs, TEQs, NDL-PCBs (34) and OCPs (35, 36) with pubertal onset and sexual maturity using multivariable interval-censored survival analyses. Lipid-standardized concentrations were used for DLCs, TEQs and NDL-PCBs, and wet-weight concentrations were used with total lipids included as a covariate in the OCP models. We initially assessed the cross-sectional associations of high vs. low BLL with pubertal onset status at study entry using adjusted logistic regression models (37), and subsequently evaluated the longitudinal association of lead with pubertal onset using multivariable Cox proportional hazard models for time to pubertal onset (20). SAS (SAS Institute, Cary NC) was used for all analyses.

Results and Discussion

Peripubertal distribution of concentrations of serum organochlorines and blood lead

Table 1 summarizes the concentrations of DLCs, TEQs, NDL-PCBs, OCPs and lead measured in RCS boys at 8–9 years old in 2003–2005. The range of serum TEQ, dioxin, furan and PCB concentrations for the 482 boys was wide, from below detection limits to very high levels, with the TEQ median exceeding by three-fold those reported in the U.S. and Europe (10, 38, 39). In the RCS OCPs also had a wide range with median serum *p,p'*-DDE and HCB concentration exceeding by three-fold and 7- to 12-fold, respectively, the U.S. and Belgium medians (40–42), while median serum β HCH concentration exceeded by 20-fold the reported LOD for U.S. adolescents (the U.S. median was the LOD) (41, 42). The median (interquartile range) BLL was 3.0 (2.0–5.0) $\mu\text{g/dL}$ (37), which is higher than among children in the U.S. (43), but lower than in China (44).

Peripubertal organochlorine chemicals, lead and growth and pubertal outcomes

Growth and development—In adjusted models (Table 2), boys in the highest quintile of Σ TEQs, Σ DLCs and Σ NDL-PCB concentrations had significantly lower mean (95% CI) BMI z-scores of -0.67 ($-1.01, -0.33$), -0.67 ($-1.01, -0.33$) and -1.04 ($-1.37, -0.71$), respectively, as compared to the lowest quintile (32). Another analysis found that boys with higher serum HCB, β HCH and *p,p'*-DDE had significantly lower mean (95% CI) BMI z-scores by -0.84 ($-1.23, -0.46$), -1.32 ($-1.70, -0.95$), and -1.37 ($-1.75, -0.98$) respectively, for the highest vs. lowest quintile (33).

Higher Σ TEQ, Σ DLC and Σ NDL-PCB concentrations were associated with lower height z-scores; however significant associations were reported only for Σ NDL-PCBs (32).

Comparison of the highest versus the lowest quintile revealed that higher serum Σ NDL-PCB concentrations were associated with lower height z-scores (mean z-score -0.41 [95% CI $-0.67, -0.14$]). Similarly, higher Σ DLCs and Σ NDL-PCBs were associated with lower HV; however, significant associations were reported only for Σ NDL-PCBs. The highest versus the lowest quintile of Σ NDL-PCBs was associated with lower mean HV of -0.19 cm/year (95% CI $-0.37, -0.01$). Σ TEQs was not associated with HV.

The highest quintile of *p,p'*-DDE was associated with a significantly lower mean (95% CI) height z-score (−0.69 [−1.00, −0.39]) and HV (−0.22 [−0.43, −0.01]) compared to the lowest quintile (33). Although the highest quintile of β HCH compared to the lowest was not significantly associated with height z-score, there was a significant trend test ($p=0.03$), suggesting that as serum β HCH increases height z-score is lower. Serum HCB was not associated with height or HV. We reported that higher peripubertal BLL ($\geq 5 \mu\text{g/dL}$) versus lower ($<5 \mu\text{g/dL}$) was associated with lower height z-score (32) (mean decrease: 0.44). Our findings suggest that peripubertal concentrations of serum dioxins, NDL-PCBs, OCPs and BLL were associated with reduced growth during adolescence.

EDCs and growth—Growth involves complex endocrine signaling pathways that can be interrupted by EDCs. Dioxins, NDL-PCBs, OCPs and lead were associated with reduced BMI and height z-scores in our cohort. Dioxins act through the aryl hydrocarbon receptor/ aryl hydrocarbon receptor nuclear translocator (AhR/ARNT) complex to regulate a number of genes involved in normal development and metabolic homeostasis (1, 45). Other compounds such as OCPs and NDL-PCBs do not bind the AhR, thus their effect may entail other mechanisms, such as disruption of thyroid hormones (1, 2, 46).

While longitudinal studies on the effects of prenatal and neonatal exposure to OCs have yielded inconsistent associations with growth, follow-up has not been through puberty to young adulthood (47–58), and we are unaware of another longitudinal study focusing on peripubertal exposure measures. In the Yu-Cheng cohort, children exposed in utero to high levels of PCBs from contaminated cooking oil were shorter and had reduced lean muscle mass than age-matched (ages 6–13 years) children (59). Prenatal PCB exposure has been associated with reduced childhood BMI (60).

In our cohort, higher peripubertal BLL was associated with lower serum insulin-like growth factor-1 at ages 11–13 years (61), suggesting that inhibition of the hypothalamic–pituitary–growth axis may be one possible pathway by which BLL affects growth. We will conduct further analysis of other hormones that regulate growth and metabolism, such as testosterone, thyroid-stimulating hormone and free thyroxine, to investigate the association of peripubertal EDCs with hormonal pathways.

Pubertal onset—In adjusted models, peripubertal serum concentrations of Σ TEQs and Σ DLCs were associated with later pubertal onset (Table 3). For Σ TEQs, after nine years of follow-up, mean age at attaining TV $> 3 \text{ mL}$ was delayed by 4.0 (95% CI −1.9, 9.8), 7.5 (95% CI 0.6, 14.4) and 11.6 months (95% CI 3.8, 19.4) for Q2, Q3, and Q4, respectively, compared to the lowest quartile (trend $p=0.003$) (34). The highest compared to lowest Σ DLC quartile was associated with an 8 month later pubertal onset (95% CI: 1.1, 15.1 months). Although not statistically significant, boys with higher peripubertal serum HCB concentrations had a later mean age of pubertal onset (35). We found no associations of serum β HCH or *p,p'*-DDE with age at pubertal onset. In contrast, higher peripubertal serum Σ NDL-PCBs were associated with an earlier mean age at pubertal onset by −3.1 (95% CI −8.9, 2.8), −5.6 (95% CI −12.3, 1.2), and −8.3 months (95% CI −16.2, −0.3) for Q2, Q3, and Q4 Σ NDL-PCBs, respectively, compared to the lowest quartile (trend $p=0.04$) (34).

High BLL ($\geq 5 \mu\text{g/dL}$) compared to low ($<5 \mu\text{g/dL}$) was associated in cross-sectional and longitudinal analyses with a 6–8 month delay in pubertal onset (hazard ratio= 0.73) (20, 37).

Sexual maturity—Similarly, we also found associations between peripubertal serum OC concentrations with later sexual maturity (34). In adjusted models, the highest compared to lowest ΣTEQ and ΣDLC quartiles were associated with later sexual maturity (95% CI) by 11.6 (17.6, 5.7) and 5.5 (11.0, -0.01) months, respectively. Similarly, boys with higher peripubertal serum HCB concentrations achieved sexual maturity a mean of 5.0 months (95% CI 0.2, 9.8) later, compared to Q1 (36). βHCH and p,p' -DDE were not associated with sexual maturity timing. However, the highest compared to the lowest quartile of $\Sigma\text{NDL-PCBs}$ was associated with earlier sexual maturity by -6.3 months (95% CI -12.2 , -0.3) (34). Our results suggest that TEQs, DLCs, and HCB may delay, while NDL-PCBs advance, male sexual maturation.

EDCs, pubertal onset and sexual maturity—The regulation of puberty involves integration of environmental and metabolic signals by the kisspeptin/GPR54 ligand receptor complex (62, 63) which regulates hypothalamic secretion of gonadotrophin-releasing hormone (GnRH) (64). This process can be affected by somatic growth and exogenous factors including diet and stress (65, 66). Pulsatile hypothalamic GnRH stimulates secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (67) to initiate puberty. During sexual maturation, LH, FSH, testosterone, insulin-like 3, and inhibin B increase dramatically and anti-Mullerian hormone declines (67).

EDCs can disrupt the neuroendocrine and hormonal pathways that are critical for the onset and normal progression of puberty via several mechanisms that have been suggested from in vitro and in vivo animal studies (4). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and dioxin-like compounds have been shown to transcriptionally regulate specific genes (1, 68, 69), which may affect pubertal onset and tempo. Several mechanisms have been suggested to describe the AhR mediated interference of steroid hormone regulated responses (70–72). TCDD can also inhibit Leydig cell proliferation and steroidogenesis (73) and suppress cyclic adenosine monophosphate production (74). The TCDD/AhR/ARNT complex has also been shown to affect androgen signaling by interacting with androgen response elements (75, 76). HCB has also been shown to disrupt androgen production and androgen receptor (AR) binding (77).

Animal models suggest that the reproductive axis is particularly sensitive to lead during specific developmental periods, with a lead-associated decrease in GnRH production (78) and inhibition of sex steroid biosynthesis resulting in delayed puberty (79). Our findings demonstrate a delay in pubertal onset in boys with higher BLL (20, 37), whereas some cross-sectional studies have found associations between lead and later pubertal onset in girls (80–82).

Some NDL-PCBs are classified as estrogenic (83, 84), and some PCBs have been shown to interfere with transcriptional activation of the AR (85). We reported that non-dioxin-like PCBs may advance the timing of male puberty. Three cross-sectional studies among Belgian adolescent boys found inconsistent associations between serum NDL-PCBs with puberty

(40, 86, 87); however, the largest study found a positive association between NDL-PCBs and puberty (40). Also, although the most recent study did not find an association between NDL-PCBs and puberty, higher NDL-PCBs were associated with higher serum testosterone and lower estradiol (87). Conversely, a US study demonstrated that exposure to PCBs, particularly the more persistent congeners, may be associated with lower testosterone levels in adolescent males (88). In our RCS we will investigate the association of peripubertal EDCs with hormonal pathways by further analysis of hormones that regulate puberty, such as testosterone, estradiol, LH, FSH and dehydroepiandrosterone sulfate.

In conclusion, the RCS is one of the few prospective cohorts that has measured childhood serum dioxin, PCB, and pesticide concentrations and blood lead levels at age 8–9 and followed participants through the pubertal transition to young adulthood. In our study we also collected data on diet, SES, and life-style indicators, allowing adjustment for these factors. A limitation of our study is that we have a single biological measurement at 8–9 years, therefore we cannot evaluate the effects of prenatal or later pubertal levels of organochlorines and lead.

Our findings suggest that the peripubertal window is vulnerable to organochlorine and lead disruption of male puberty and growth. The RCS is ongoing with follow-up for young adult males in progress, and includes collection of semen samples (89), analysis of longitudinal hormonal data, and the study of epigenetic markers in leukocytes and sperm.

Since 1997, in parallel with our ongoing research studies, the Russian regional and local governments led environmental remediation and social programs in Chapaevsk and built a new children's hospital in 2009. During this period, mean dioxin TEQs in breast milk declined 3.8-fold from 41.1 pg TEQ/g lipid to 10.9 pg TEQ/g lipid in 1998 and 2007, respectively (90). The average serum concentrations of TEQ and sum of PCB congeners among eight adult women decreased by 30% (from 36 to 25 pg TEQ/g lipid) and 19% (from 291 to 211 ng/g lipid), respectively, over 2000–2009 (91). The infant mortality rate in Chapaevsk decreased from 27.6 per 1,000 live birth in 1993–96 to 7.4 in 2011–13. As a result of these research and remediation activities, Chapaevsk was designed a member of the World Health Organization network “Healthy Cities” in 2015.

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Figure 1. Recruitment (A) and retention (B) flow diagrams for subjects in RCS

^aUsed town records to identify boys in Chapaevsk that were 8 to 9 years old in 2003 to 2005

^bNot born in Chapaevsk, likely to relocate, or chronic illness

^cIdentified post-enrollment as orphans, excluded from analysis

^d18 years – age for recruitment to military service in Russia

Table 1

Distribution of peripubertal serum concentrations and TEQs of organochlorines and blood lead among boys in the Russian Children's Study^a

Characteristic	n	25th	Median	75 th	Maximum
TEQ (pg TEQ/g lipid) ^b					
TCDD ^c	482	1.3	2.8	3.9	44.9
PCDD TEQ	482	4.5	8.2	13.5	89.8
PCDF TEQ	482	3.0	4.2	6.9	154.3
Co-PCB TEQ ^d	482	4.5	6.4	9.4	67.2
Total TEQ	477	14.4	21.1	33.2	174.7
Concentration (pg/g lipid) ^b					
PCDD	482	93	136	189	1237
PCDF	482	27	39	57	1083
Co-PCB ^d	482	126	181	249	2067
Total PCDD/PCDF/C-PCB	482	278	362	499	2963
Total NDL-PCB, (ng/g lipid) ^e	477	164	249	393	4248
HCB (ng/g lipid)	355	107	158	246	2660
β-HCH (ng/g lipid)	355	112	167	270	2860
p,p'-DDE (ng/g lipid)	355	187	284	492	9370
Lead, (µg/dL)	481	2.0	3.0	5.0	31.0

^aBurns, Williams (10), Hauser, Sergeyev (37), Lam, Williams (41)

^bSamples below the LOD (limit of detection) were assigned a value = LOD/ 2

^cThe median LOD for TCDD was 0.60 pg/g lipid; 123 (26%) of TCDD values were less than this LOD.

^dSum of co-planar PCB TEQs (IUPAC congeners: 77, 81, 126, 169)

^eSum of non-coplanar PCBs (IUPAC congeners: 18, 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 118, 128, 138/158, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196/203, 201, 206)

Longitudinal associations of peripubertal serum organochlorine concentrations and TEQs with growth among boys in the Russian Children’s Study.

Table 2

Serum Organochlorines	Mean difference in growth outcomes in the highest quintile vs lowest quintile (Q5 vs Q1)					
	Height z-score ^a Estimate (95% CI)	P-value for trend	BMI z-score ^a Estimate (95% CI)	P-value for trend	Height velocity Estimate (95% CI)	P-value for trend
TEQs, dioxin-like compounds and PCBs, lipid-standardized ^b						
ΣTEQs	−0.21 (−0.48, 0.06)	0.07	−0.67 (−1.01, −0.33)	<0.001	−0.04 (−0.22, 0.15)	0.39
ΣDioxin-like compounds	−0.22 (−0.48, 0.05)	0.13	−0.67 (−1.01, −0.33)	<0.001	−0.13 (−0.31, 0.05)	0.06
ΣNondioxin-like PCBs	−0.41 (−0.67, −0.14)	0.01	−1.04 (−1.37, −0.71)	<0.001	−0.19 (−0.37, −0.01)	0.01
Organochlorine pesticides, lipid-standardized ^c						
HCB	−0.19 (−0.49, 0.11)	0.18	−0.84 (−1.23, −0.46)	<0.001	−0.05 (−0.25, 0.16)	0.19
βHCH	−0.28 (−0.59, 0.02)	0.03	−1.32 (−1.70, −0.95)	<0.001	−0.03 (−0.23, 0.18)	0.47
p,p'-DDE	−0.69 (−1.00, −0.39)	<0.001	−1.37 (−1.75, −0.98)	<0.001	−0.22 (−0.43, −0.01)	0.03

^aWorld Health Organization age-adjusted z-scores (25)

^bBurns, Williams (32), ages 8–12 years; n=461

^cBurns, Williams (33), ages 8–13 years; n=350

Table 3

Longitudinal associations of peripubertal serum organochlorine concentrations and TEQs with pubertal development outcomes among boys in the Russian Children's Study

Serum Organochlorines	Mean shift in age at pubertal outcomes, Quartile 1 vs. Quartile 4			
	Pubertal Onset TV > 3 mL Mean shift in months (95% CI)	P-value for trend	Sexual Maturity TV 20 mL Mean shift in months (95% CI)	P-value for trend
TEQs, dioxin-like compounds and PCBs, lipid-standardized ^a				
ΣTEQs	11.6 (3.8, 19.4)	0.003	11.6 (5.7, 17.6)	<0.001
ΣDioxin-like compounds	8.1 (1.1, 15.1)	0.01	5.5 (−0.01, 11.0)	0.04
ΣNondioxin-like PCBs	−8.3 (−16.2, −0.3)	0.04	−6.3 (−12.2, −0.3)	0.06
Organochlorine pesticides, wet-weight				
HCB	4.7 (−1.4, 10.9) ^b	0.06	5.0 (0.2, 9.8) ^c	0.02
βHCH	1.4 (−4.9, 7.6) ^b	0.56	3.6 (−1.3, 8.5) ^c	0.07
<i>p,p'</i> -DDE	3.3 (−3.1, 9.7) ^b	0.36	2.5 (−2.5, 7.4) ^c	0.35

^aBurns, Lee (34), ages 8–18 years; n=473

^bLam, Williams (35), ages 8–17 years; n=346

^cLam, Williams (36), ages 8–17 years; n=349