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Review

Relationships of putative endocrine disruptors to human sexual maturation and thyroid activity in youth

Lawrence M. Schell [a,b,*], Mia V. Gallo [a]

[a] University at Albany, Department of Anthropology, A&S 237, 1400 Washington Avenue, Albany, NY, United States
[b] University at Albany, Department of Epidemiology and Biostatistics, School of Public Health. One University Place, Room 131, Rensselaer, NY, United States

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ABSTRACT

Endocrine disruption has become a significant human health concern, but is difficult to study outside of the laboratory for several reasons including the multiplicity of exposures, the difficulty in assessing each exposure, and the variety of possible outcomes among human populations. This review summarizes our studies of the relationships of measured persistent organic pollutants (PCBs, *p,p′*-DDE, HCB and mirex), and heavy metals (lead and mercury), to outcomes directly related to thyroid function and sexual maturation. These studies were conducted in a sample of Native American youth from the Akwesasne Mohawk community. The participants were first studied during puberty (10–16.9 years of age) and then at approximately 18 years of age. Results from these studies show that PCB levels are positively related to TSH and negatively to free T4. Further, these effects are conditioned by breastfeeding history. Anti-thyroid peroxidase antibody levels also are related to PCB levels suggesting elevated risk of autoimmune disease among the exposed. Earlier age at menarche is associated with higher PCB levels while risk of delay is associated with higher lead levels. Some evidence that the timing of exposure produces different effects is presented, and the level of exposure in the participants suggests that effects observed may be relevant to a considerable proportion of the US population. Further investigations are warranted to determine effect thresholds and mechanisms.

Contents

* Corresponding author. A&S 237, University at Albany, 1400 Washington Ave., Albany, NY 12222, United States. Tel.: +1 518 442 5761; fax: +1 518 442 4563.
E-mail address: l.schell@albany.edu (L.M. Schell).

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1. Introduction

Widespread concern over the potential effects of persistent organic pollutants (POPs) has been growing for decades, largely due to scientific information from studies of wildlife, carefully controlled laboratory experiments, and associations in human populations between POP exposures with some health related outcomes. Persistent organochlorines are lipophilic, slow to metabolize, and bioaccumulate in animal, bird, and human fat tissues over a lifetime. Exposure to these pollutants usually occurs through ingestion of contaminated water, food, or inhalation of air, and can occur prenatally through passage across the placenta, or postnatally by lactation or food consumption [1].

In recent years, scientific publications and the popular press have raised concern that certain POPs, specifically polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), and *p,p′*-dichlorophenyldichloroethylene (DDE), a metabolite of DDT, may have adverse effects on mammals, including humans, and other wildlife by disrupting the endocrine system [2–8]. These exogenous agents can mimic or antagonize natural hormones in the body that are instrumental in controlling myriad functions including growth and development, maturation, metabolism, and reproduction [9].

Additionally, compared to adults, the fetus and child have different sensitivities and reactivities to toxicants [10]. The most obvious examples are exposures to methyl mercury, to alcohol and to diethylstilbestrol which produce quite different effects in the fetus than in the adult [11]. Thus, there is concern that exposure to POPs and consequent hormonal disruption in a fetus or young child may be irreversible, and produces physiological programming with a wide range of possible effects that may arise later in life.

Laboratory evidence of endocrine-like effects is extensive, showing alterations in synthesis, metabolism, distribution, and clearance [12–26]. Predicting effects of toxicants in humans is problematical. While animal studies usually involve single exposure models, humans are subject to daily, multichemical exposures. Also, doses used in laboratory studies may not be comparable to humans' exposures.

Experimentation on humans in this area is understandably unethical. Studies of human populations must consider the multiple exposures to toxicants (in contrast to the single exposure models most common in laboratory work), the developmental stage(s) of the sample, and the myriad effects possible from exposure at different development stages and from different levels of exposure. Furthermore, most studies of human populations are retrospective making exposure assessment problematic: summary measures cannot distinguish exposures by stage of development and measures that capture recent exposure cannot assess exposure at potentially early, critical stages of development.

Despite all the limitations associated with studies of human populations, the results from laboratory studies and the reality of potential effects on human health warrant continued research with humans. Over the past 15 years we have conducted two studies in partnership with the St Regis/Akwesasne Mohawk community, Hogansburg, NY. In these projects we were able to measure multiple toxicants and thereby capture some of the exposure complexity of human populations. By focusing on youth and adolescents, we were able also to address questions of sexual development, among others. Here we describe the results of these investigations that address the issue of human health effects. This article summarizes our publications reporting analyses of thyroid hormone levels, sexual maturation, and related outcomes in relation to specific persistent organic pollutants, all based on a study of young members of the Akwesasne Mohawk Nation who have experienced exposure from local industrial sources of pollutants through contamination of local waterways. Three main questions were addressed by this research: 1) Are current PCB levels of youth associated with levels of hormones involved in thyroid hormone activity (TSH, TT4, T3, FT4)? 2) Is current PCB level of young adults associated with a marker of autoimmune disease, specifically anti-thyroid antibody level? and, 3) Is variation in current PCB levels of youth associated with variation in sexual maturation, specifically, age at menarche? For each of these questions we also seek to learn if specific PCB congeners are more closely associated with the outcomes than other PCB congeners, and if so, what is the meaning of these differences with regard to timing of exposure?

2. Methods

2.1. Sample

The Akwesasne Mohawk Nation is situated on the St. Lawrence River with territory abutting New York State, Ontario and Quebec, Canada. Residents of the community live within the boundaries of the St. Regis Mohawk Reservation/Reserve, and in neighboring communities that are part of the traditional Mohawk territory, including Bombay, Fort Covington, Hogansburg, Massena, Rooseveltown (NY), and in Cornwall, Ontario. Recent reports indicate a population of approximately 12,000–13,000 [27–29], however, Akwesasne is not a federally censused population and published estimates of the Akwesasne community's population size vary.

Several industrial complexes are located near Akwesasne, a result of industrial development along the St. Lawrence River which began in the 1950s. The Akwesasne Mohawk Nation is located downstream of a National Priority Superfund Site (General Motors Central Foundry Division), and two New York State Superfund Sites (Reynolds Metal Company and Aluminum Company of America); all aluminum foundries, that have contaminated the St. Lawrence River and its three tributaries with PCBs, *p,p′*-DDE, HCB, mirex, and heavy metals (mercury and lead). In the mid-1980s, local species of fish, birds, amphibians and mammals were found to have levels exceeding the US Food and Drug Administration's tolerance limits for human consumption [30,31], leading to advisories against the consumption of fish and game in the late 1980s and early 1990s [28,32]. It is believed that postnatal exposure to toxicants is largely from the consumption of locally caught fish [33]. However, there is some evidence that exposure from other sources occurs also [1].

2.2. Data collection

Two cross-sectional studies were conducted by the University at Albany and the Akwesasne Mohawk Nation. The first, the Mohawk Adolescent Well-Being study (MAWBs), was conducted between 1995 and 2000, and involved 271 youth between the ages of 10 and 16.99 years (48% males; 52% females). The second study, the Young Adult Mohawk study (YAWBs), was a follow-up of participants in the earlier project. Participants were between 17 and 20 years of age, and numbered 153 individuals. Of the MAWBs participants who were eligible, 25% were lost to follow-up and 9% refused to participate. The participation rate was 66%. It differed slightly by gender (males 40% and females 60%); the loss of male participants was greater. Table 1 illustrates the number of participants (by sex) for both studies with regard to the published articles summarized in this review.

Written informed consent was obtained from the children's parents/guardians and assent was gained by the participating minor. The study protocols were reviewed and approved by the Institutional Review Board at the University at Albany, S.U.N.Y. Details of recruitment and sampling have been reported earlier for MAWBS [11] and YAWBS [34]. In brief, eligibility required not being a twin, not diagnosed with a psychological or physical impairment, and not diagnosed with fetal alcohol syndrome or effects. These last two were disqualifiers for a component study investigating the effects of toxicants on cognition [35], that are not described here. Sample sizes for the analyses described below vary slightly depending on the outcome and variables needed as covariates in multivariate analyses.