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Exposure to polychlorinated biphenyls and the thyroid gland – examining and discussing possible longitudinal health effects in humans

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ABSTRACT

Background: Many previous studies have dealt with the effect of polychlorinated biphenyls (PCBs) on the thyroid gland, but their findings are inconsistent. One problem of these studies has been their use of cross-sectional designs.
Objectives: The aim of the current study is to investigate longitudinal effects of PCBs on the thyroid gland, focusing on: morphological changes in thyroid tissue (i.e. thyroid volume), changes in thyroid hormones and in thyroid antibodies.
Methods: A total of 122 individuals (M_{age}=44.7) were examined over a period of four years (t^1 until t^4). Medical history was collected via interviews, an ultrasound examination was performed and blood samples were taken to determine plasma PCB levels, thyroid stimulating hormone (TSH), free triiodthyronine (fT3), free thyroxine (fT4), thyroid peroxidase antibodies (TPOab), thyreoglobulin antibodies (TGab) and thyroid-stimulating hormone receptor antibodies (TSHRab). Rank correlation coefficients and mixed effect models were performed controlling for age and total lipids.
Results: There were negative correlations between higher chlorinated biphenyls and fT3, cross-sectionally as well as longitudinally. We also found an interaction effect of higher-chlorinated PCBs over time for fT4 as well as TSHRab. In case of high exposure, a decrease in fT4 and an increase in TSHRab level were found over time. In regards to the other variables, our findings yielded no clear results in the examined time period.
Conclusion: This is the first study to shows a PCB-related effect on fT3, fT4 and TSHRab over a four year period. The data also suggest that morphological and antibody findings remain inconsistent and do not allow for unambiguous interpretation.

1. Introduction

Previous research has often reported the harmful effects of environmental toxins on the thyroid gland (e.g. Boas, 2006; Patrick, 2009). One of these harmful toxins are polychlorinated biphenyls (PCBs). PCBs are a group of 209 congeners of a chemical that consists of two phenyl rings with different degrees of substituted chlorine atoms. According to their degree of chlorination and their chemical properties, PCBs are classified as lower-polychlorinated biphenyls (LPCBs), higher-polychlorinated biphenyls (HPCBs) and dioxin-like polychlorinated biphenyls (dlPCBs). These substances are synthetic chemicals that are not naturally occuring, but the frequent use, until their ban in the 1980s, has led to an increased concentration in the environment. Especially PCBs with a higher degree of chlorination have a high persistence and exist in the environment over an extended period of time. This is one reason why the general population shows a background exposure with PCBs even today (Becker et al., 2002; Schettgen et al., 2015, 2011). A further source of PCB exposure is via contaminated air in houses which were built with materials containing PCBs (Harrad et al., 2009; Schettgen et al., 2012a). Nevertheless, currently the

Abbreviations: PCBs, Polychlorinated Biphenyls; LPCBs, Lower Chlorinated Biphenyls; HPCBs, Higher Chlorinated Biphenyls; dlPCBs, Dioxin-like Polychlorinated Biphenyls; ThV, Thyroid Volume; TSH, Thyroid Stimulating Hormone; T4, Thyroxine; fT4, Free Thyroxine; T3, Triiodthyronine; fT3, Free Triiodthyronine; rT3, Reverse Triiodthyronine; D1–D3, Deiodinase Type 1–Type 3; TPOab, Thyroid Peroxidase Antibodies; TGab, Thyreoglobulin Antibodies; TSHRab, Thyroid-Stimulating Hormone Receptor Antibodies; NTIS, Non-Thyroidal-Illnes-Syndrome; r_s, Spearman's Rank Correlation Coefficient; t^1–t^4, Cross Section 1–Cross Section 4

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environmental exposure to PCBs via food and drinking water or via contaminated air is much lower than occupational exposure via repairing or recycling old technical machines. In such cases, PCBs can be inhaled via contaminated air or absorbed through direct skin contact (Faroon et al., 2003). The resulting PCB body burden has often been investigated in relation to adverse somatic health effects (e.g. Longnecker et al., 1997) as well as mental health effects (e.g. Gaum et al., 2014). A healthy thyroid gland is essential for both, physical and mental health. Previous research has often dealt with PCB-related health consequences, specifically on the thyroid gland. Thereby, the negative PCB-related health effects were often reported in relation to morphological changes of thyroid tissue, changes in thyroid hormones as markers for thyroid function and metabolism as well as changes in thyroid antibodies as markers for a potential autoimmune reaction.

Regarding the morphological changes of human thyroid tissue, Langer and colleagues are the only researchers who used ultrasound examination to investigate thyroid tissue after PCB exposure. The authors consistently found a higher thyroid volume with a higher PCB body burden across several studies (e.g. Langer et al., 2007a, 2005, 1998). Significantly higher prevalence rates of goiter and nodules were only found in men who lived in a higher burdened area in comparison to a low burdened area (Langer et al., 2003). In a later study however no associations were found between PCB exposure and the prevalence rates of nodules; neither for men nor for women (Langer et al., 2007a). Thus, findings on morphological changes of the thyroid gland in relation to PCB exposure are unclear and need further exploration.

Morphological abnormalities may be a symptom of a disturbed thyroid function, but are not highly indicative markers. Therefore, the second perspective considers actual thyroid functionality and metabolism by assessing potential changes in thyroid hormones – namely thyroid stimulating hormone (TSH), thyroxine (T4) and triiodthyronine (T3). An association between PCB exposure and thyroid hormones has often been reported in animal studies, such as in PCB-exposed rats whose thyroid gland was found to show a reduced response reaction to a TSH injection (Byrne et al., 1987). Furthermore, also in rats and in mice, a dose related decrease in T3 and T4 was reported after exposure to PCBs (e.g. Kato et al. 2004; Hallgren et al., 2001). These results have not yet been consistently replicated in human studies (Hagmar, 2003). For example, in elderly participants who were environmentally exposed to PCBs, no association between PCBs and the thyroid hormones TSH, free T4, total T4 and total T3 could be found (Bloom et al., 2014; Rylander et al., 2006). One past study reported a weak negative effect between PCBs and total T3 for women (Hagmar et al., 2001a), while no effects between PCBs and thyroid hormones were detected in men (Hagmar et al., 2001b). Weak negative correlations were also found for PCBs with TSH and fT3, but these effects were no longer significant for TSH or even inversely related for fT3 after controlling for age, BMI and gender (Donato et al., 2008). Thus PCB effects on thyroid hormones seem weak and complex and suggest that individual confounding factors may have an effect on the data.

Abnormal hormone levels might be an indicator of an impaired thyroid function or disturbed thyroid metabolism, but they can also be a symptom of autoimmune thyroiditis. Therefore as a third aspect, we address thyroid-related antibodies. Only a few studies so far have addressed thyroid-specific antibodies after PCB exposure in humans. While Murai et al. (1987) found that no effects for thyroid antibodies between PCB-exposed "Yusho"-patients and a non-exposed group, Langer et al. (2007a, 2005) report PCB-related signs of autoimmune thyroiditis including elevated antibody levels. For example, men with higher PCB exposure show more signs of a thyroid specific autoimmune disease (i.e. hypo-echogenicity, high thyroid peroxidase antibodies and high TSH) than men with low PCB exposure. The authors could not find differences in these signs of autoimmune disease in women. Since research regarding PCB effects on thyroid-related autoimmune reaction is rare, further attention needs to be paid to thyroid antibodies as a sign for thyroid-related autoimmune reaction.

In sum, results of previous studies are inconsistent for thyroid-specific PCB effects in humans related to thyroid morphology, metabolism and thyroid related autoimmune reaction. To the best of our knowledge all studies use cross-sectional designs. Possible long-term effects of PCBs on thyroid gland may therefore remain undetected (Hagmar, 2003). Especially in adults, the thyroid gland has a high and long-term ability to compensate disturbances in relation to its functionality (Brent, 2010). Furthermore autoimmune diseases develop over a long period of time.

Considering past research, we hypothesize that a positive association exists between PCBs and thyroid volume, as well as between PCBs and TSH. Furthermore we assume a negative correlation between PCBs and the thyroid hormones fT3 and fT4, but a positive association between PCBs and the thyroid peroxidase antibodies (TPOab), the thyroglobulin antibodies (TGab) and the TSH receptor antibodies (TSHRab). To test these hypotheses, the present study deals with the impact of PCB body burden and its effect on the thyroid gland over a period of four years. For a better comparison with past research we also tested our hypotheses cross-sectionally.

2. Methods

2.1. Design

We used a four-year longitudinal within-subjects design with a one year time lag between the different cross sections. The four cross sections are labeled with the abbreviations t^1, t^2, t^3 and t^4; in the following text, tables and figures. All hypotheses were tested cross-sectionally with the whole sample, as well as longitudinally with mixed effect models.

2.2. Study population

All the participants in the current study took part in the medical surveillance program HELPcB (Health Effects in high Level exposure to PCB). This program was developed for occupationally PCB-exposed employees of a transformer and capacitor recycling company, alongside their relatives and employees of surrounding companies. For more details about the HELPcB program see Kraus et al. (2012). A total of 269 employees of the recycling company and surrounding companies and 31 relatives participated in the HELPcB program at least once (N=300). Out of the total sample, 252 participants were male (84%) and 48 were female (16%). The mean age of all participants was 44.7 years at the first cross section (SD_{age}=13.1; range: 19–83 y) and the mean period of exposure was 113.4 months ($SD_{exposure}$=141; range: 1–577 m). The mean body weight was 86.9 kg (SD =17.8) at t^1, 86.8 kg (SD =17.2) at t^2, 86.8 kg (SD =16.8) at t^3 and 88.9 kg (SD =17.4) at t^4. The mean amount of smoking was 16.7 pack years (SD =18.9) at t^1, 15.6 pack years (SD =18.6) at t^2, 14.6 pack years (SD =17.9) at t^3 and 15.7 pack years (SD =18.6) at t^4. Out of the total 300 participants, 178 did not participate in all four cross sections or dropped out of the program. The most common reason for not participating in all cross sections was that the examination date fell during working hours and the participants were not allowed to take leave from work. The second most common reason was because of acute illness such as a cold. Altogether, 267 individuals participated at t^1, 216 at t^2, 180 at t^3 and 150 at t^4. Since we applied a longitudinal design, we only considered the 122 individuals who participated at all four cross sections. All participants had to provide an