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Hyperpigmentation and higher incidence of cutaneous malignancies in moderate-high PCB- and dioxin exposed individuals

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ABSTRACT

Polychlorinated biphenyls (PCB) are well known persistent and toxic environmental pollutants.

Our aim was to identify effects of moderate-high exposure to dioxin-like (dl) and non-dioxin-like (ndl)-PCBs on the skin in order to provide more insight in the pathophysiological effects of these compounds.

We performed a dermatological examination on 92 former workers from a transformer recycling company with known elevated serum PCB and/or dioxin (polychlorinated dibenzo-*p*-dioxin/polychlorinated dibenzo-*p*-furan (PCDD/F)) levels. In addition, we performed a skin cancer screening over a period of seven years (2010–2016) on resp. 268, 271, 210, 149, 92, 129 and 79 participants.

We found a higher incidence of acne and malignancies of the skin (malignant melanoma, basal cell carcinoma and mycosis fungoides) in the workers compared to normal population.

The probability of having hyperpigmentation on the skin was statistically significantly higher in workers with higher sumPCBs- (OR:1.09(1.12–2.17)), dioxin-like (dl)-PCBs- (OR:1.56(1.12–2.17)) and dioxin (PCDD/Fs) (OR:1.09(1.02–1.16)) levels. Age was a confounding factor in this model.

Formation of hyperpigmentation could be an indicator for (moderate-high) exposure to toxic compounds like PCBs.

The higher incidence of cutaneous malignancies found in the workers might be associated with PCB- and dioxin exposure, warranting further investigation on larger cohorts.

1. Introduction

Polychlorinated biphenyls (PCB) are notorious and highly persistent environmental pollutants. They were produced for their fire resistance and low electrical conductivity in many products like dielectric isolators, dihydraulic oils, paint and plasticizers (de Voogt). As a side-product, highly toxic dioxins (polychlorinated dibenzo-*p*-dioxin/polychlorinated dibenzo-*p*-furan (PCDD/Fs) are formed. Although PCB production is forbidden in Europe since 1977, in Germany the usage of PCBs in chemical- and mining industry has been reported to be longer (Kredel, 2011). Large amounts of PCBs have been released since the 30 s. As a result, these toxic compounds are wide spread and levels are measureable in blood of human beings worldwide (Rappe, 1984; Rappe et al., 1985).

Exposure in the general population occurs mainly through ingestion (90%), however, other roots of exposure (inhalation and through dermal contact) play an important role during occupational exposure (Baars et al., 2004). The half life is estimated 3–9 years depending on the type of congener and is dose dependent (Grandjean et al., 2008).

Due to their hydrophobic nature PCBs are primarily stored in adipose tissue and liver.

There are 209 congeners differing in degree of chlorination and in the location of the chlorine atoms on the two benzene rings. Separate congeners can exert different effects depending on their three-dimensional structure (dioxin-like and non-dioxin-like). Dioxin-like congeners can exert a certain kind of toxicity through the aromatic hydrocarbon Receptor (AhR) (Denison and Nagy, 2003). This is a multiprotein complex and a cytosolic transcription factor, which is in normal condition inactive. Bonding this receptor induces the expression of cytochrome P450 by induction of the CYP1A1, CYP1A2, and CYP1B1. In addition, other xenobiotic metabolizing enzymes, transporter proteins and transcription of several genes are stimulated by activation of AhR

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(Denison and Nagy, 2003; Nebert and Karp, 2008).

Skin is a major target organ of toxic effects of PCBs and dioxin as well as signaling organ for the toxicity of these compounds (Leijs et al., 2018).

After the Yusho incident (Japan, 1968: accidental leakage of PCBs and PCDFs into rice oil destined for human consumption) for example, a disease, characterized by acne-like eruptions, pigmentation of the skin, and eye discharge appeared. More than 1800 patients have been registered as having Yusho (Yoshimura, 2003). Similar to Yusho, about 2000 people on Taiwan Island ingested rice oil contaminated with PCBs and PCDFs in 1978. The exposed population developed chloracne, hyper-pigmentation, peripheral neuropathy and other symptoms, which were later called Yucheng disease (Rogan et al., 1988). Another well-known more recent example of chloracne after dioxin exposure is the poisoning of Victor Yushchenko, the former president of Ukraine (Saurat et al., 2012).

Effects of lower, background, PCB exposure include endocrinological, immunological and neurological disturbances (Leijs et al., 2009, 2012; Lundqvist et al., 2006; Pang et al., 1999; Leijs et al., 2017). Dermatological effects of occupational PCB and dioxin exposure in western countries are only sporadically documented (Budnik et al., 2014).

In spring 2010, high internal exposures for PCBs were discovered in workers of a transformer recycling company in Germany, where PCB-contaminated material was not handled according to proper occupational hygiene. A prospective surveillance program for (former) workers, their family members and relatives and subjects working or living in the surroundings of the company was initiated (Schettgen et al., 2012).

In this study, as part of the surveillance program, our aim is to identify effects of dioxin-like (dl) and non-dioxin-like (ndl)-PCBs on the skin in order to provide more insight in the pathophysiological effects of exposure to these compounds.

2. Materials and methods

2.1. Participants and procedures

Participants of the present study took part in the medical surveillance program HELPcB (Health Effects in High-Level Exposure to PCB). This program was initiated in 2010 after human biomonitoring revealed increased blood levels of PCB in workers of a capacitor and transformer recycling company, where PCB-contaminated material was not handled according to proper occupational hygiene. Elevated PCB levels were not only discovered in the workers, but due to contamination also in their relatives, as well as in workers of surrounding companies (Schettgen et al., 2012). Further details of the surveillance program are published elsewhere (by Kraus et al. (2012)). The surveillance program was approved by the ethics committee of the University Hospital at RWTH Aachen University. Participation in the survey was completely voluntary and participants could leave HELPcB any time without any consequences.

For the present study, which was performed in 2014, 92 participants (75 male, 17 female) who met a dermatological screening examination in 2014 were included. In addition, a dermatological screening on skin malignancies was performed in 2010–2016 on resp. 268, 271. 210, 149, 92, 129 and 79 participants of the surveillance program.

The participants in 2014 underwent a dermatological screening by the same dermatologist (M.M.L) in order to detect possible dermatological problems following PCB and dioxin exposure (chloracne, other acneiform lesions, comedones, hyperpigmentations, porphyria cutanea tarda, Meibomian gland lesions, nail deformities, hyperkeratosis, and malignancies of the skin).

The participants were asked to fill in a questionnaire to define possible confounding factors in dermatological outcomes (hair-, skin- and eye- color, smoking status, alcohol drinking status, age, medical history, and history of exposure to other chemicals such as pesticides in agriculture or arsenic or heavy metals).

2.2. PCB and dioxin (PCDD/F) Exposure

Initial plasma PCB and blood levels of dioxins (PCDDs/Fs) were determined in 2010 (and for 19 participants who entered the surveillance program later in 2011) using gas chromatography with mass spectrometry (GC-MS) (Schettgen et al., 2011). As classified by the human biomonitoring commission of the German environmental agency (Federal-Environmental-Agency, 1999) the non-dioxin like indicator congeners PCB 28, 52, 101, 138, 153, 180 and their sum were calculated. As representatives of the dioxin like congeners PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189 were examined. If only 10% or less than 10% of the measurements exceeded the limit of detection (LOD), the congener was discharged from further investigation. This was the case for PCB 77, 81, 126 and 169. The LOD for every congener was 0.01 μg/L blood plasma.

For all participants serum cholesterol and serum triglycerides were available. As suggested by Bernert et al. (2007) we used the CDC-short formula to calculate total blood lipids (TL) and used TL for lipid standardization of the PCB plasma levels.

In 2010 (and for some of the participants in 2011) levels of 17 dioxins (PCDD/Fs) were measured in the serum of the participants using gas chromatography with high resolution mass spectrometry (HR-GC-MS). 7 PCDDs: (2,3,7,8-TetraCDD; 1,2,3,7,8-PentaCDD; 1,2,3,4,7,8-HexaCDD; 1,2,3,6,7,8-HexaCDD; 1,2,3,7,8,9-HexaCDD; 1,2,3,4,6,7,8-HeptaCDD; OctaCDD) and 10 PCDFs: (2,3,7,8-TetraCDF; 1,2,3,7,8-PentaCDF; 2,3,4,7,8-PentaCDF; 1,2,3,4,7,8-HexaCDF; 1,2,3,6,7,8-HexaCDF; 2,3,4,6,7,8-HexaCDF; 1,2,3,7,8,9-HexaCDF; 1,2,3,4,6,7,8-HeptaCDF; 1,2,3,4,7,8,9-HeptaCDF; OctaCDF) were measured. Preliminary results of 23 of the participants are published elsewhere.

2.3. Statistical examinations

For descriptive statistics, a frequency analysis was conducted for all study variables. Due to the circumstance that the dependent variable 'Hyperpigmentation' is dichotomous and that PCB biomonitoring data is per se right skewed and left censored, non-parametric correlation and logistic regression was conducted for inferential analysis. In accordance with the work of O'Brien et al. (2015) we decided to use lipid adjusted PCB values as a predictor and not to use blood lipids as covariate (Model II for environmental chemicals).

In SPSS, crosstabs were used to determine the incidence rate ratio for non-melanoma skin cancer. Elevated PCB- or dioxin levels were the risk factor, and non-melanoma skin cancer the outcome. The total amount of studied subjects with elevated PCB levels (over a period of 7 years) were taken as the (PCB and dioxin) exposed group. In the calculation of the incidence rate ratio, this group was compared with the incidence for the normal German population (with unknown background PCB exposure) in 2010 (Rudolph et al., 2015). Incidences were period adjusted.

Correlations between sum indicator PCB, dl-PCBs, total sum PCBs and dioxin (PCDD/F) levels were calculated using Spearman's correlation coefficient.

A Kendall-Tau-b correlation was used to examine whether there is an influence of the potential confounding variables age, hair color, eye color, sun exposure in childhood and as adult, sunbed use, smoking habits and alcohol consumption on Hyperpigmentation. To answer the question whether hyperpigmentation is affected by the internal PCB burden of the participants, we build a logistic regression model for every PCB congener with hyperpigmentation (or atypical naevi, amount of naevi, hyperkeratosis, nail dystrophy, basal cell carcinomas, papules/comedos/pustules) ('yes' or 'no') as dichotomous dependent variable, the lipid adjusted PCB level of the PCB congeners, sum PCB or dioxins as predictor and the age of the participants in 2014 as covariate.