NeuroToxicology 63 (2017) 106–119

Contents lists available at ScienceDirect

NeuroToxicology

Full Length Article

# Neuropsychological effects of occupational exposure to polychlorinated biphenyls

B. Fimm[a,*], W. Sturm[a], A. Esser[b], T. Schettgen[b], K. Willmes[a], J. Lang[b], P.M. Gaum[b], T. Kraus[b]

[a] RWTH Aachen University, Department of Neurology, Pauwelsstraße 30, D-52074 Aachen, Germany
[b] RWTH Aachen University, Institute of Occupational Medicine, Pauwelsstraße 30, D-52074 Aachen, Germany

ARTICLE INFO

*Article history:*
Received 26 October 2016
Received in revised form 20 September 2017
Accepted 21 September 2017
Available online 22 September 2017

*Keywords:*
Neuropsychology
Verbal fluency
Motor function
Polychlorinated biphenyls
Dopamine
HELPcB,

ABSTRACT

In the context of a health surveillance program for former PCB-exposed workers of a transformer and capacitor recycling company in Germany, their family members, employees of surrounding companies and area residents a broad range of cognitive functions covering attention, executive processing, reasoning, memory and motor performance was examined. The study aimed at identifying potential adverse effects of PCB load on cognitive functions. Detailed analysis of PCB burden of the participants revealed rather high correlations of lower and higher chlorinated as well as dioxin-like PCBs. Nearly one half of the participants exhibited increased burden in all three PCB classes whereas only 33 out of 237 participants did not show any increased PCB burden. Thus, data analysis followed a two-fold strategy: (1) Based on studies providing data on PCB exposure of the German general population the PCB burden of every participant was classified as normal (percentile rank PR <95) or increased (PR ≥95). Increased burden with respect to lower (LPCBs) and higher chlorinated (HPCBs) as well as dioxin-like (dlPCBs) PCBs was assumed if a participant showed at least one congener surpassing the PR95 criterion for the respective congener class and (2) Overall plasma PCB level per congener class was used as measure of PCB load. In a multivariate approach using structural equation modelling and multiple regression analysis we found a significant impact of PCBs on word fluency and sensorimotor processing irrespective of the measure of PCB burden (PR95 criterion or overall plasma level). However, no effect of PCB burden on memory, attention, and cognitive flexibility could be demonstrated. Particularly, an increase of LPCBs was associated with an overall reduction of verbal fluency of letter and semantic word generation as well as word production based on a single or two alternating criteria. In addition, participants with increased burden of LPCBs exhibited a time-on-task effect in terms of a stronger decline of performance with increasing duration of the verbal fluency task. Moreover, we found adverse effects of HPCBs on Aiming and of dlPCBs on Line Tracking. Results are discussed in terms of (1) a decrease of cerebral dopamine (DA) with non-coplanar PCBs resulting in an impact on fronto-striatal cerebral structures subserving verbal fluency and motor processing, (2) a PCB-induced reduction of norepinephrine leading to the time-on-task effect with verbal fluency, and (3) adverse effects of PCBs on dopaminergic receptors in the cerebellum resulting in impaired fine motor function.



## 1. Introduction

Polychlorinated biphenyls (PCBs) are persistent organic compounds that have been widely used as flame retardants, coolants or heat transfer agents in electrical transformers, hydraulic fluids, plasticizers or as additives in pesticides, paints, adhesives, sealants, carbonless copy paper, organic diluents, and plastics (Vreugdenhil and Weisglas-Kuperus, 2005). They differ in the position and number of chlorine atoms (Frame et al., 1996) and comprise 209 possible congeners. Higher chlorinated congeners (HPCBs) in general are metabolized more slowly and therefore accumulate in fatty tissues (Schettgen et al., 2011) leading to higher persistence and potential increase with age. On the other hand, lower chlorinated PCB congeners (LPCBs) with 5 chlorine atoms or less are characterised by higher volatility and lower potential for bioaccumulation (Schettgen et al., 2011). Furthermore, PCBs are classified as dioxin-like (dlPCBs; coplanar PCBs with no or only one chlorine atom on the ortho-position) and non-dioxin-like

* Corresponding author.
*E-mail address:* fimm@neuropsych.rwth-aachen.de (B. Fimm).

https://doi.org/10.1016/j.neuro.2017.09.011

congeners. The total quantity of PCBs produced worldwide from 1929 to the 1980s, when most countries reduced or stopped the production, has been estimated at approximately 1.5 million metric tons (WHO, 2000; Voogt and Brinkman, 1989). Production and use of these substances was stopped worldwide in line with the Stockholm convention, which became effective in 2004 (Schettgen et al., 2015). Thus, the exposure level and body burden exerted by PCBs has declined over the years. However, due to long persistence of various congeners and dietary intake, there still is a considerable PCB background burden in the population, especially of HPCBs. Exposure to LPCBs is mainly caused by indoor air-contamination and inhalation uptake due to their use in the construction of public buildings (Liebl et al., 2004; Schettgen et al., 2012)

PBCs have repeatedly been shown to exert toxic effects on the cerebral and endocrine system and to suppress immunological mechanisms in animal studies (Faroon and Olson, 2000; Faroon and Ruiz, 2011). Acquired PCB burden in adults has been demonstrated in various studies. In an adult sample, Peper et al. (2005) found subtle attenuation of emotional well-being and attentional function in 30 employees exposed to indoor air contaminated with LPCBs from elastic sealants in a school building. Further evidence on neurotoxic effects of PCBs in adults stems from studies examining big samples being exposed to industrially caused PCB pollution. In 271 Mohawk adolescents living in a region along the St. Lawrence river Newman et al. (2006, 2009) demonstrated moderate association of persistent, non-persistent, dioxin-like and non-dioxin-like PCB burden with long-term memory performance (delayed recall and long term retrieval). Furthermore, impaired auditory processing was related to the level of persistent congener burden. Most importantly, the correlation of non-persistent congeners with three cognitive test scores (delayed recall, long term retrieval and verbal comprehension/lexical knowledge) was interpreted to be a consequence of continuing or recent environmental exposure to PCBs sufficient to result in detectable cognitive decrements. Haase et al. (2009), examining the same St. Lawrence cohort, found threshold effects of PCB for executive functioning and fine motor behaviour and finger dexterity required to manipulate pegs on the grooved pegboard test. However, finger tapping and static motor steadiness did not show any relationship to PCB load. These threshold effects were largely observable within the older age (37–79 years) group. The authors conclude that PCB exposure may exacerbate the normal aging process on certain aspects of cognitive and motor processes. Lin et al. (2008) conducted a retrospective cohort study among members (age ≥ 60 years) of an existing cohort in mid central Taiwan (Yucheng cohort) being exposed to PCBs due to ingestion of contaminated cooking oil about 25 years earlier. Compared to an age-, sex- and neighbourhood-matched control group they found a decline of working memory and learning in women, whereas executive, motor and sensory performance did not differ from the control group. Further evidence for PCB-induced memory deficits comes from a study by Fitzgerald et al. (2008) examining 253 persons between 55 and 74 years living along contaminated sectors of the upper Hudson River in the State of New York. They describe decreased immediate memory and increased symptoms of depression with increasing PCB burden.

In sum, past research gives first hints that PCBs may have adverse effects on cognitive and motor functions. However, results are rather inconsistent. In the present study, being part of the HELPcB (Health Effects in high Level exposure to PcB) surveillance program for highly exposed individuals (Kraus et al., 2012), a broad range of cognitive functions covering attention, executive processing, reasoning, memory and motor performance as well as depressive symptoms was examined. Because of heterogeneous results in the literature we applied a comprehensive test battery to be able to detect even subtle neuropsychological deficits.

## 2. Methods

### 2.1. Participants

The participant group consisted of PCB-exposed workers of a transformer and capacitor recycling company in Germany, of their family members, employees of surrounding companies and area residents. Schettgen et al. (2012) have given more detailed information on the participant sample in the HELPcB surveillance program. 237 participants underwent comprehensive neuropsychological examination, 119 of whom were PCB-exposed workers, 10 were family members, 104 were employees in companies nearby and 3 were area residents. Sex was asymmetrically distributed (207 male, 30 female), mean age was 43.96 years (SD 12.59 years; range: 19–83 years). Considering their educational background, 41 participants had graduated from high school (12–13 years of schooling), 72 participants graduated after 10 years, 116 participants graduated after 8–9 years of schooling and 8 participants did not graduate from school (see Table 1a).

Due to different first language and resulting problems with verbal tests 35 participants did not work on the Regensburg Word Fluency Test, another 4 participants with missing values on verbal fluency were not sufficiently motivated or suffered from fatigue or attention problems. Furthermore, 11 participants had missing values in other tests due to fatigue (n = 1), deficits in alphabetical knowledge (n = 3; leading to problems in TMT-B), reduced comprehension of test instructions (n = 2; TAP Working memory), motor problems (n = 1), problems in TAP Divided Attention due to increased nervousness (n = 1) and impaired auditory processing (n = 1), reduced fitness following surgery (n = 1), and technical problems (n = 1). Taken together, reduced German language skill was the main reason for excluding participants in the verbal neuropsychological tests. Consequently, multivariate statistical analysis (see structural equation models below) were computed with only 187 participants exhibiting complete data sets (see Tables 1b and 2).

**Table 1a**
Distribution of age and education of the participant sample (n = 237). Age and education prove to be independent ($\chi2(15) = 21.9$; exact $p = .129$). Cell contents y/x represent male (y) and female (x) participants.

| | | Education | | | | Total |
|---|---|---|---|---|---|---|
| | | <8 schoolyears | 8–9 schoolyears | 10 schoolyears | 12–13 schoolyears | |
| **Age (years)** | **19–29** | 2/0 | 16/1 | 19/2 | 4/3 | 47 |
| | **30–39** | 1/0 | 15/1 | 15/0 | 3/4 | 39 |
| | **40–49** | 4/0 | 27/2 | 13/2 | 15/2 | 65 |
| | **50–59** | 1/0 | 33/4 | 12/5 | 5/2 | 62 |
| | **60–69** | 0 | 14/2 | 3/0 | 3/0 | 22 |
| | **70–83** | 0 | 1/0 | 1/0 | 0 | 2 |
| **Total** | | 8 | 116 | 72 | 41 | 237 |