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# Plasma polychlorinated biphenyl and organochlorine pesticide concentrations in dementia: The Canadian Study of Health and Aging

Thierry Comlan Marc Medehouenou [a,b], Pierre Ayotte [c,d,e], Pierre-Hugues Carmichael [b], Edeltraut Kröger [a,b], René Verreault [b,c], Joan Lindsay [c,f], Éric Dewailly [c,d,e], Suzanne L. Tyas [g,h], Alexandre Bureau [c,i], Danielle Laurin [a,b,*]

[a] Faculté de pharmacie, Université Laval, Quebec City, Québec, Canada
[b] Centre d'excellence sur le vieillissement de Québec, Santé des populations et pratiques optimales en santé, Centre de recherche du CHU de Québec, Quebec City, Québec, Canada
[c] Faculté de médecine, Département de médecine sociale et préventive, Université Laval, Quebec City, Québec, Canada
[d] Axe Santé des populations et pratiques optimales en santé, Centre de recherche du CHU de Québec, Quebec City, Québec, Canada
[e] Laboratoire de toxicologie, Institut national de santé publique du Québec, Quebec City, Québec, Canada
[f] Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[g] School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario, Canada
[h] Department of Psychology, University of Waterloo, Waterloo, Ontario, Canada
[i] Centre de recherche de l'Institut universitaire en santé mentale de Québec, Quebec City, Québec, Canada

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ABSTRACT

*Background:* Even though polychlorinated biphenyls (PCBs) and organochlorine (OC) pesticides are recognized as neurotoxicants, few studies have investigated their associations with dementia. Here, we assess associations of plasma PCB and OC pesticide concentrations with all-cause dementia and Alzheimer's disease (AD).
*Methods:* Analyses are based on data from the Canadian Study of Health and Aging, a population-based study of men and women aged 65+ years at baseline. PCB and OC pesticide concentrations were measured in 2023 participants who had complete clinical evaluations and blood samples; 574 had dementia, including 399 cases of AD. Concentrations were log-transformed and used as continuous variables in logistic regression models to assess their individual associations with dementia and AD.
*Results:* After adjustment for blood collection period, total plasma lipids, age, sex, education, apolipoprotein E e4 allele (ApoE4), tobacco and alcohol use, rural/urban residence, and comorbidities, elevated plasma PCB concentrations were not associated with increased prevalence of dementia and AD. Elevated concentrations of some OC pesticides and metabolites such as hexachlorobenzene, *cis*-nonachlor and 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane were significantly associated with a reduced prevalence of dementia. A significant reduced prevalence of AD was also observed with elevated hexachlorobenzene concentrations. Other OC pesticides and metabolites were not associated with the prevalence of dementia or AD. No effect modification by sex and ApoE4 was observed for either dementia or AD.
*Conclusions:* Elevated plasma PCB and OC pesticide concentrations were not associated with higher prevalence of all-cause dementia and AD. The possibility of modest reductions in prevalence with specific OC pesticides remains to be further investigated given the cross-sectional design of this study.


## 1. Introduction

Organochlorines (OCs), including polychlorinated biphenyls (PCBs) and OC pesticides, are ubiquitous and persistent environmental contaminants that accumulate in lipid tissues of living organisms (Li et al., 2006). Experimental studies have shown that PCBs and OC pesticides cause adverse effects on the central nervous system, suggesting potential neurotoxic effects on humans (Mariussen and Fonnum, 2006). Few cross-sectional (Fitzgerald et al., 2008; Haase et al., 2009; Schantz et al., 2001; van Wendel de Joode et al., 2001) and prospective (Lin et al., 2008) epidemiologic studies have linked PCBs and OC pesticides to neurocognitive and neurobehavioral impairment in older adults. Dementia and its most common subtype, Alzheimer's disease (AD), are characterized by cognitive deficits.

The etiology of AD is still unknown although several genetic and environmental risk factors have been identified (Chouliaras et al., 2010; Maloney et al., 2012; Marques et al., 2011). Even though PCBs and OC pesticides are recognized as neurotoxicants and thus potential environmental contributors to AD, little is known about their effects on the risk

* Corresponding author at: Centre d'excellence sur le vieillissement de Québec, Hôpital du Saint-Sacrement, 1050 chemin Sainte-Foy, Local L2-30, Quebec City, Québec G1S 4L8, Canada. Tel.: +1 418 682 7511x4832; fax: +1 418 682 7998.
*E-mail address:* Danielle.Laurin@pha.ulaval.ca (D. Laurin).

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of AD. Over the last decades, few studies have investigated their associations with dementia or AD. One case report suggested a relationship between occupational exposure to a PCB mixture (Aroclor 1260) and the development of dementia with features similar to AD (Troster et al., 1991). Another study from the National Institute for Occupational Safety and Health databases showed an increased standardized mortality ratio for dementia in women highly exposed to PCBs, but not in men (Steenland et al., 2006). A cohort study in an agricultural community suggested significant increased risk estimates for dementia and AD among pesticide-exposed individuals; however, the increased risk estimates were non-significant among those exposed to OC pesticides (Hayden et al., 2010). In the latter two studies, the use of exposure assessments based on job–exposure matrices or detailed questionnaires in person, which are prone to bias, limits the validity of the results.

To date, no epidemiologic study has examined the association of plasma concentrations of PCBs and OC pesticides with clinically assessed cases of dementia and AD. The use of such circulating concentrations yields more valid and reliable information and allows identification of specific PCB congeners and OC pesticides. The aim of the present study was to assess the associations of plasma PCB and OC pesticide concentrations with the prevalence of all-cause dementia and AD using data from the Canadian Study of Health and Aging (CSHA).

## 2. Materials and methods

### 2.1. Study population and dementia assessment

The CSHA is a national cohort study of older Canadians designed to examine prevalence, incidence and risk factors for dementia. Eighteen research centers across the country and one coordinating center were involved. Methodological details have been described elsewhere (Lindsay et al., 2004; The Canadian Study of Health and Aging Working Group, 1994). The baseline examination was carried out in 1991–1992 (CSHA-1) with two follow-up examinations performed five and ten years later. The three phases received approval from institutional ethics committees in all participating centers; participants and/or family representatives gave written consent at each phase.

In CSHA-1, a random sample of 10,263 men and women, representative of the Canadian population aged 65 and over, was drawn from Enumeration Composite Records in Ontario and from Medicare lists in the other provinces for 36 urban and surrounding rural areas where roughly 60% of Canadians were living. Institutionalized participants were randomly selected from residents in stratified random samples of institutions in each region. The study excluded the Yukon and the Northwest Territories, Indian reserves and military units. Of the study participants, 9008 were living in the community and 1255 in institutions. Community-living participants were screened for dementia using a cut-off of 77/78 on the 100-point Modified Mini-Mental State (3MS) examination (The Canadian Study of Health and Aging Working Group, 1994). Participants who screened positive (3MS score <78), a random sample of those who screened negative (3MS score >77) and all participants living in institutions were invited to attend an extensive standardized three-stage clinical evaluation. A nurse readministered the 3MS, collected information on medication use, and obtained the participant's medical and family histories from a relative. A physician solicited information on the participant's medical history and performed a standardized clinical and neurological examination. Non-fasting blood samples were drawn for laboratory tests (required if dementia or delirium was presumed) or collected for future analyses (optional) at the end of the examination. Finally, a psychometrist administered a neuropsychological test battery to participants with a 3MS score of 50 and over; results were interpreted by a neuropsychologist. Preliminary diagnoses of all-cause dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised criteria (DSM-III-R) were made independently by the physician and the neuropsychologist, who subsequently arrived at a final diagnosis in a consensus conference. Final diagnoses also included AD according to the National Institute of Neurological and Communicative Disorders and Stroke — Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Vascular dementia (VaD), other specific and unclassifiable dementias, no cognitive impairment, and cognitive impairment with no dementia (CIND) were diagnosed according to DSM-III-R and the International Classification of Diseases, 10th revision criteria.

Information on risk factors was collected at baseline (CSHA-1) with a self-administered risk factor questionnaire (RFQ) covering sociodemographic and lifestyle characteristics as well as family and medical histories. Participants with no dementia were invited to complete the RFQ at home and return it by mail. As part of a first case–control study with prevalent cases of AD, the same RFQ was administered to proxies of prevalent cases of participants with dementia, and to proxies of controls (The Canadian Study of Health and Aging, 1994).

All participants initially evaluated were contacted in 1996–1997 (CSHA-2) to assess changes in health status and functioning. CSHA-2 participants underwent a similar diagnostic process (screening and clinical evaluation) as in CSHA-1. If participants had been clinically examined at CSHA-1, they were automatically invited to CSHA-2 clinical examination. CSHA-2 diagnoses were made blinded to CSHA-1 diagnoses. To account for the modification of diagnostic criteria over the interval between CSHA-1 and CSHA-2, final diagnoses for dementia and AD were made for all participants according to the criteria used in CSHA-1 as well as revised according to the more recent criteria (Lindsay et al., 2004). All participants who were clinically assessed were asked to provide blood samples, except for those who previously gave blood in CSHA-1.

The last phase of CSHA (CSHA-3) took place in 2001–2002. The cut-off for screening with the 3MS was increased to 89/90 to focus on more complete identification of participants with cognitive impairment. Participants unable to complete the neuropsychological evaluation or who had received a diagnosis of CIND or dementia from the neuropsychologist were asked to attend the clinical examination. The final diagnosis was made according to the same processes and diagnostic criteria as those used in CSHA-2 (Lindsay et al., 2004). All participants who were clinically assessed in CSHA-3 were asked to provide blood samples, except for those who previously gave blood either in CSHA-1 or CSHA-2.

### 2.2. Blood sampling

Nine out of the 18 study centers in CSHA-1 and all study centers in CSHA-2 and CSHA-3 participated in the creation of a blood bank for future analyses. Plasma fractions were divided into aliquots and stored at −20 °C at the National Microbiology Laboratory, initially part of Health Canada in Ottawa, and more recently part of the Public Health Agency of Canada in Winnipeg, Canada. In total, blood samples were available for 2119 participants: 422 out of the 2914 clinically assessed in CSHA-1, 1312 out of the 2305 in CSHA-2, and 385 out of the 1386 in CSHA-3. Of the 2119 participants, 96 had to be excluded because of lack of consensus diagnosis or stored plasma, leaving 2023 participants for chemical and statistical analyses (Fig. 1). The measurement of OCs received approval from the research ethics review board of the *CHU de Québec* (*Hôpital de l'Enfant-Jésus*), Quebec City, Canada.

### 2.3. Laboratory analyses

Plasma OC concentrations were determined as described previously (Medehouenou et al., 2011) at the *Laboratoire de toxicologie* of the *Institut national de santé publique du Québec*, which is accredited under ISO 17025 by the Standards Council of Canada, and participates regularly in many international quality control programs (Raaschou-Nielsen et al., 2005). Briefly, 15 PCB congeners (nos. 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 163, 170, 180, 183, 187) and 11 OC pesticides or their metabolites [aldrin, mirex, α-chlordane, γ-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, β-hexachlorocyclohexane (β-HCH), hexachlorobenzene (HCB), 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane