

INCREASED DIOXIN/PCB BODY BURDEN IN DIABETICS: FINDINGS IN A POPULATION-BASED STUDY IN BELGIUM

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Introduction

Although the average dioxin and PCB burden has declined during the last decades in most industrialised countries, some groups of the general population, especially the elderly, still show an elevated body burden of these pollutants as a result of their dietary habits and current or past exposures¹. For these groups, dioxins and PCBs might remain a matter of concern in view of the recent epidemiological evidence of a possible implication of dioxins and PCBs in diabetes^{2,3}.

The findings reported in this study provide further evidence of a link between dioxins or PCBs and diabetes in environmentally-exposed populations.

Methods

After approval by the local Ethical Committee, the study was performed on a total of 257 subjects (142 women and 115 men) who were recruited in 2000/2001 in five areas of Belgium⁴. The studied groups included: (i) 58 subjects aged 25 to 67 years living within the vicinity of an iron and steel plant (Cockerill); (ii) 52 subjects aged 26 to 71 years living around a waste dumping site (Mont-Saint-Guibert); (iii) 33 subjects aged 33 to 65 years recruited from the vicinity of a municipal solid waste incinerator (MSWI) in an industrial area (Pont-de-Loup); (iv) 51 subjects aged 21 to 80 years living in the vicinity of a MSWI in a rural area (Thumaide) and (v) 63 subjects aged 33 to 66 years recruited as referents living in rural areas of the Ardenne (Southern Belgium). All subjects were recruited on a volunteer basis via a mail targeting adult subjects with a long residence time in the same area and regularly consuming locally produced foods. The two incinerators of Pont-de-Loup and Thumaide had been in operation since 1978 and 1980, respectively. After having given their informed consent and filled a detailed questionnaire, the volunteers provided approximately 200-250 ml of blood under fasting conditions in order to evaluate the body burden of dioxins and PCBs. The seventeen 2,3,7,8 substituted polychlorinated dibenzodioxin/dibenzofuran congeners (PCDD/Fs), four dioxin-like non-*ortho*-PCBs (coplanar PCBs; IUPAC n° 77, 81, 126 and 169) and 12 PCB markers (IUPAC n° 3, 8, 28, 52, 101, 118, 138, 153, 180, 194, 206 and 209) were quantified by GC-HRMS on the lipid fraction of serum⁵. All results were reported per gram fat. Concentrations of dioxins and coplanar PCBs were expressed in toxic equivalents (TEQ) using the 1998 international toxic equivalent factors of the World Health Organisation.

Information about the health status of the subjects was obtained by the questionnaire. A total of nine subjects reported to suffer from diabetes (5 women and 4 men), which was either controlled by hypoglycemics (n=6), by insulin (n=1) or by diet alone (n=2). These diabetic

subjects were residents of the vicinity of the MSWI in the rural area (n=3), the iron and steel plant (n=2), the waste-dumping site (n=2) and the control area (n=2).

The differences between diabetics and their controls were assessed by the Student's t-test applied on log-transformed data (inverse transformation for BMI). A stepwise multiple linear regression model was used to identify determinants of dioxin, coplanar PCB and 12 PCB markers concentrations and after adjustment for other covariates, all case and control dioxin and PCB values were again compared by the Student's t-test. Odds ratios were calculated on the total population divided into two groups using as cut-off the 90th percentile of adjusted dioxin, coplanar PCB and 12 PCB markers concentrations (SAS procedures, Enterprise Guide 2.0).

Results

As shown in Table 1, subjects with diabetes were well matched with their controls for age, BMI and serum lipids. There were no significant differences in body weight loss and fat intake between controls and diabetics. The mean serum levels of PCDD/Fs, coplanar PCBs and 12 PCB markers were significantly increased in diabetics compared to the rest of the population.

Table 1. Characteristics and mean dioxin and PCB concentrations of subjects

	Diabetics (n=9)	Controls (n=248)
Age (years)	56.0 (52.6-59.4)	51.5 (50.3-52.8)
BMI (kg/m ²)	26.2 (23.0-30.4)	25.6 (25.1-26.2)
Serum lipids (g/l)	7.85 (6.67-9.25)	7.38 (7.18-7.58)
Weight loss	3 (33%)	30 (12%)
Fat intake (g/week) [†]	252 (153-416)	181 (169-194)
PCDD/Fs (pg TEQ/g fat)	46.6 (34.7-62.5)	25.2 (23.6-26.8)*
Coplanar PCBs (pg TEQ/g fat)	16.2 (9.47-27.7)	7.2 (6.65-7.73)*
Total TEQ [‡] (pg TEQ/g fat)	64.2 (46.7-88.3)	32.8 (30.8-35.0)*
12 PCB markers (ng/g fat)	652 (512-831)	402 (383-423)*

Values are geometric mean (95% confidence interval (CI)) except age (arithmetic mean and 95% CI), BMI (body mass index, inverse transformed) and weight loss (number and percentage of subjects who lost weight within the year before examination). [†]Fat intake was calculated from the questionnaire (consumption of poultry, bovine and swine products). [‡]Total TEQ: PCDD/Fs and coplanar PCBs. * Difference between diabetics and controls was statistically significant ($p < 0.05$) by t-test.

These findings were confirmed by multiple regression analyses testing the influence of diabetes, age, BMI, area of residence, smoking habits, weight loss, fat intake and fish consumption. Diabetes emerged as a significant determinant (partial $r^2=0.03$) of PCDD/Fs levels which also correlated positively with age (partial $r^2=0.16$), residence around the MSWI in the rural area (partial $r^2=0.11$), BMI (partial $r^2=0.02$) and fat intake (partial $r^2=0.015$). The serum levels of coplanar PCBs were also positively correlated with diabetes (partial $r^2=0.04$) together with age (partial $r^2=0.11$), BMI (partial $r^2=0.09$), residence around the rural MSWI (partial $r^2=0.05$) and fish consumption (partial $r^2=0.03$). Diabetes also correlated positively with the 12 PCB markers (partial $r^2=0.02$) together with age (partial $r^2=0.24$) and fat intake (partial $r^2=0.06$). Figure 1 illustrates the increase in total TEQ and 12 PCB markers in the serum of diabetic subjects after adjustment for other covariates. The body burden of these pollutants in diabetics was on average 62 % ($p=0.0005$)

and 39 % ($p=0.0067$) higher than that of controls, respectively. This increase of the body burden of dioxins and PCBs in diabetics was however not congener-specific as all congeners were found to rise in diabetics to approximately the same extent (results not shown). Of note, congener patterns found in diabetics exhibited fingerprints corresponding to background environmental contamination only and did not show any increase of the congeners characterising the Belgian 1999 PCB/dioxin incident⁶.

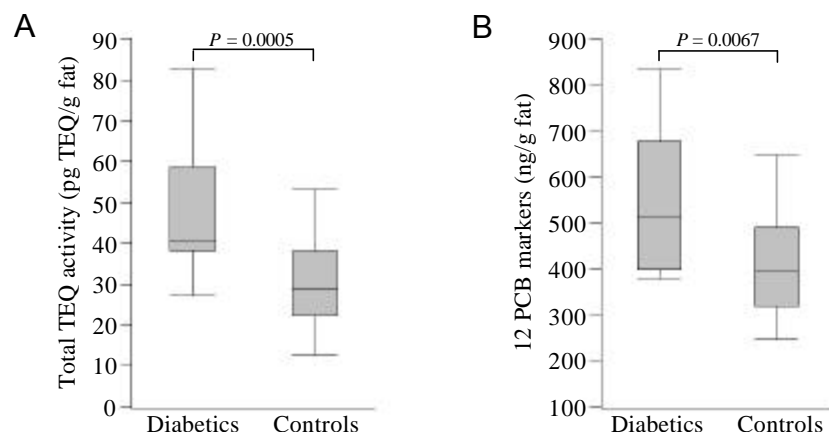


Figure 1. Distribution of serum dioxin and PCB concentrations in diabetic and non-diabetic subjects. Data are box plots displaying the 5th, 25th, 50th, 75th and 95th percentiles. A. Total TEQ activity (PCDD/Fs + coplanar PCBs), pg TEQ/g fat. B. 12 PCB markers, ng/g fat. Diabetics and controls were compared by the Student's t-test.

To further explore the link between diabetes and dioxins or PCBs, we estimated the probability of being diabetic by dividing the total population into two groups using as cut off the 90th percentile of the dioxin, coplanar PCB and 12 PCB markers concentrations adjusted for other covariates. The odds ratios were statistically significant in the top deciles, reaching values of 5.07 [95 % confidence limit (CL), 1.18 – 21.7] for dioxins, 13.3 [3.31 – 53.2] for coplanar PCBs and 7.58 [1.58 – 36.3] for 12 PCB markers.

Discussion

Although based on a relatively small number of cases, the increase of the serum levels of both dioxins, coplanar PCBs and 12 PCB markers in diabetics are surprisingly highly significant. In addition, for these three categories of pollutants, a significant increase of the risk of diabetes was found in the most exposed subjects (top decile). All these observations remained statistically significant after adjustment for possible confounders (age, BMI, fat intake, fish consumption or place of residence) identified by multivariate analysis.

These associations between diabetes and dioxins or PCBs, however, should be interpreted with caution since the direction of the causality still remains to be established. There are presently no data allowing to determine whether the higher levels of dioxins and PCBs in diabetes truly reflect a higher exposure to these pollutants, which in turn may contribute to diabetogenesis, or whether they are merely the consequence of diabetes-induced metabolic perturbations facilitating the accumulation of these pollutants. Indeed, diabetes is associated with a variety of metabolic

changes that quite conceivably could alter the metabolism of dioxins and PCBs and could influence the distribution and elimination of these lipophilic compounds. The possibility of a slower elimination of dioxins in diabetes is, however, not supported by a study on Vietnam veterans in whom no difference in TCCD half-life was found between diabetic and non-diabetic patients⁷. In our study, concentrations of serum lipids in diabetics were similar to controls and there were no alterations of the dioxin and PCB patterns in the diabetics' serum fat, which also tends to argue against the hypothesis of a slower biotransformation of these compounds in diabetes. Finally, diabetes could be hypothesized to increase the serum fat to adipose tissue ratio of dioxins and PCBs, but whereas a difference in tissue distribution of these compounds is usually associated with a shift in the congener patterns, this was not found to be the case in our study.

The second hypothesis is that dioxins or PCBs might play a role in the aetiology of diabetes. Such a possibility is suggested by several epidemiological studies linking higher dioxin or PCB body burden to an increased risk of diabetes or modified glucose metabolism. Some of these studies concern industrial workers or populations having experienced high levels of exposure⁸⁻¹⁰, but others relate to general population chronically exposed to background levels of these pollutants^{3,11,12}. Interestingly, it has been hypothesized² that dioxins or PCBs could promote diabetes by interaction with PPAR γ , a ligand-activated transcription factor controlling lipid metabolism and homeostasis, that is linked with diabetes¹³. If such an interaction could be demonstrated, it would provide a plausible biological explanation for associations found in epidemiological studies.

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