

## **Dietary exposure to dioxins and polychlorobiphenyls and breast cancer risk, all-cause mortality and cancer-specific mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC)**

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### **INTRODUCTION**

Dioxins and polychlorinated biphenyls (PCBs) are known to be highly persistent in the environment and have long-range transport, leading to a ubiquitous pollution. This group of persistent organic pollutants is known to be carcinogenic and can exhibit endocrine-disrupting properties. Due to bioaccumulation along the food chain, the main route of exposure in the general population is through diet. Most of the epidemiological evidence relies on occupational cohorts and accidental mass food poisoning, but studies in the general population are scarce.

Two prospective cohorts (E3N and Swedish Mammography Cohort) observed no relationship between dietary exposure to dioxins and PCB-153 and breast cancer risk, but the Swedish study found a positive association between PCB-153 and cardiovascular mortality risk.

The aim of the present study was 1) to evaluate dietary intakes for 17 dioxins and 35 PCBs in the large-scale European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and 2) to investigate the association between these contaminants and breast cancer risk, all-cause mortality and cancer-specific mortality

### **METHODOLOGY**

EPIC is a large prospective cohort that has enrolled 370 000 women and 150 000 men, aged 35–69, recruited between 1992 and 2000 in 23 research centres across 10 European countries. Dietary and lifestyle data have been collected at baseline through validated questionnaires. Dietary intakes for 17 dioxins and 35 polychlorobiphenyls were assessed through a combination of EPIC food consumption data and food contaminant levels from the European Food Safety Authority (EFSA) monitoring programs.

Associations between the sum of dioxins and PCBs and breast cancer risk and mortality were estimated using multivariate Cox regression. Analyses included 318 607 women including 13 241 with invasive breast cancer (median follow-up: 14.9 years) and 541 390

adults including 46 627 deaths (median follow-up: 17.4 years) for mortality analyses. Non-linear associations were assessed with cubic splines. Multiple sensitivity and subgroup analyses were conducted with further adjustments on main food contributors for dioxins/PCBs, by EPIC countries, for different periods of time for contamination data and for middle bound and lower bound scenarios.

## RESULTS

Dietary intakes of dioxins, dioxin-like PCBs (DL-PCBs) and six non-dioxin-like PCBs (6NDL-PCBs) were not associated with the incidence of breast cancer; Hazard Ratios (HRs) for an increase of one standard deviation: HR<sub>dioxins</sub> = 1.00 (0.98-1.02), HR<sub>DL-PCB</sub> = 1.01 (0.98-1.03) and HR<sub>6NDL-PCB</sub> = 1.01 (0.99-1.03).

For all-cause mortality, a non-linear U-shaped association was demonstrated for dioxins (P<sub>non-linearity</sub> <0.0001), DL-PCB (P<sub>non-linearity</sub> = 0.0001) and 6NDL-PCBs (P<sub>non-linearity</sub> <0.01) with a reduced risk of mortality in quintile analyses. For cancer mortality, there was no association in the quintile analyses for dioxins but a reduction in cancer mortality was observed for DL-PCBs and 6NDL-PCBs, with a non-linear association: DL-PCB (P<sub>non-linearity</sub> = 0.006) and 6NDL-PCBs (P<sub>non-linearity</sub> = 0.007).

For breast cancer risk and mortality, the results remained similar when the analyses were run separately per country, after adjustment or stratification for main contributing food group to PCB and dioxin intake (fish, dairy products or vegetables), several markers of the nutritional quality of the diet, after exclusion of incident cases in the first five years and a middle/lower bound scenarios.

## DISCUSSION

The analyses in this European cohort do not show any association between dietary intake of dioxins and PCBs and the occurrence of breast cancer, which corroborates the results of the Swedish Mammography Cohort and of a previous analysis in the French cohort E3N. The analyses in EPIC suggest an inverse, nonlinear, U-shaped association between dietary exposure to dioxins and PCBs and all-cause and cancer mortalities. This U-shaped relationship could be explained by the phenomenon of hormesis, with a toxic effect at low and high doses, in particular for certain dioxins and PCBs which are endocrine disruptors.

The limitations of this study are the one-time collection of food data, and the fact that the contaminant data does not date from the same year as the food consumption which may give rise to non-differential classification errors of exposure and therefore weaken relationships.

On the other hand, this study is the largest study ever conducted in the general population with a follow-up time of more than 15 years on dietary exposure to these persistent organic pollutants which allows for a great variability of dietary exposure and the assessment of the long-term effects