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A pharmacokinetic analysis and dietary information are necessary to confirm or reject the hypothesis on persistent organic pollutants causing type 2 diabetes

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HIGHLIGHTS

- Dioxins with long half-lives accumulate throughout the entire lifetime.
- Pharmacokinetic models predict the measured concentrations in populations.
- Dioxin concentrations in the body are predicted by age, animal source food and BMI.
- Dioxins may confound the role of ample animal source food in causing diseases.
- Diet and kinetics are vital in claiming causal roles of persistent pollutants in diseases.

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ABSTRACT

A number of studies have found an association between the concentrations of persistent organic pollutants (POP) and type 2 diabetes. Causality has remained uncertain. This study describes the pharmacokinetic behavior of PCDD/Fs (polychlorinated dibenzo-*p*-dioxins and dibenzofurans) both in a theoretical model based on elimination rate constants, and in a group of 409 adult surgical patients with known PCDD/F concentrations and dietary information. A model assuming 10% annual decrease in past PCDD/F intake, predicted the measured profile of TEQ (toxic equivalents) in the patient population fairly well. The dominant determinant of PCDD/F level was age, and the level in patients was also associated with consumption of animal source products. Predicted daily intakes correlated with diet, but also with body mass index (BMI), indicating that high BMI was preceded by high consumption of foods containing PCDD/Fs. The results suggest that a third factor, e.g. high intake of animal source foods, could explain both higher levels of POPs in the body and higher incidence of type 2 diabetes, and BMI is not sufficient in describing the confounding caused by diet. Thus, to fully address the causality between POPs and type 2 diabetes, careful studies considering the pharmacokinetics of the studied compounds, and including the analysis of food consumption, are needed.

1. Introduction

A number of mainly cross-sectional studies have been published, associating persistent organic pollutants (POPs) with various diseases, particularly with type 2 diabetes (e.g. Lee et al., 2006, 2007; Rignell-Hydbom et al., 2007; Airaksinen et al., 2011; Huang et al., 2015; reviewed by Kuo et al., 2013; Taylor et al., 2013; Magliano et al., 2014; Ngwa et al., 2015). The association has been reported stronger among obese persons than among non-obese

Abbreviations: BMI, body mass index; CDD, chlorinated dibenzo-*p*-dioxin; CDF, chlorinated dibenzofuran; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; Hp, hepta; Hx, hexa; O, octa; PCBs, polychlorinated biphenyls; PCDD/Fs, polychlorinated dibenzo-*p*-dioxins and dibenzofurans; Pe, penta; POP, persistent organic pollutants; T, tetra; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxic equivalency factor; WHO, World Health Organization; WHO-TEQ, toxic equivalencies according to WHO.

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persons (Lee et al., 2010). A few longitudinal studies have also been published (e.g. Turyk et al., 2009; Lee et al., 2011; Wu et al., 2013; Suarez-Lopez et al., 2015; reviewed by Magliano et al., 2014; Ngwa et al., 2015). However, studies on the mechanism of action have been disappointing (Ngwa et al., 2015; Turyk et al., 2015) and often highly hypothetical (Lee and Jacobs, 2015).

There are some questions that need to be resolved, before the observed associations can be considered causal. The most obvious concerns are, *first*, why type 2 diabetes is increasing now although POP intakes have decreased during the last decades to 10–20% of those in 1970s (minor impact could, of course, be overwhelmed by a major factor), *second*, why effects of similar magnitude are reported between type 2 diabetes and a long list of POPs in completely different chemical classes such as dioxins, PCBs, and organochlorine pesticides, and *third*, why similar effects are seen within populations exposed to high or low POP concentrations, but not between the groups (Steenland et al., 2001; Ngwa et al., 2015). All in all, the literature is so far quite complex and confusing (Taylor et al., 2013; Ngwa et al., 2015).

In none of the studies so far a relation between the pharmacokinetics of POPs and fat intake or the amount of fat in the body was discussed. In the Ranch Hand Study, plasma concentration of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) was correlated with type 2 diabetes, and a closer examination of the results suggested reverse causality, i.e. imminent diabetes influencing the concentrations of TCDD (Kerger et al., 2012). The authors conclude that the absence of any significant difference in diabetes incidence between Ranch Hand veterans and comparison veterans argues against the presumption of a causal relationship between TCDD and type 2 diabetes. In other words, there was an association within each group of veterans, but no significant difference between the groups, regardless of very different plasma concentrations of TCDD. Contrary to the Ranch Hand study, no increase in type 2 diabetes was seen in the NIOSH (National Institute for Occupational Safety and Health) industrial cohort although the TCDD concentrations were almost tenfold (Steenland et al., 2001).

A thorough meta-analysis revealed that associations between diabetes and TCDD are seen in cross-sectional studies with plasma TCDD levels less than 10 pg/g lipid, but not in cohort studies with much higher TCDD levels (Goodman et al., 2015). It was concluded that the available data do not indicate a causal relationship (Goodman et al., 2015).

Thus, the requirements of Bradford Hill criteria of causality are not yet met (Hill, 1965), and the observed associations might rather suggest that TCDD serves as a proxy of something else that correlates with type 2 diabetes.

In some studies, reverse correlation – type 2 diabetes changing the pharmacokinetics of POPs – has been discussed (Longnecker and Daniels 2001; Lee et al., 2010), but it has not been considered that the higher levels of POPs in the body and higher incidence of type 2 diabetes could both be correlated with and possibly caused by a same third factor. The possibility was qualitatively hinted in the review of Taylor et al. (2013), but not quantitatively discussed. A recent review commented that findings are equivocal, and good-quality research is urgently needed (Jaacks and Staimez, 2015).

Another related recent hypothesis is that POPs might contribute to the "obesity epidemic" (Reaves et al., 2015). There is indeed an association between some but not all POPs and body mass index (BMI) or waist circumference (Elobeid et al., 2010; Dirinck et al., 2011), although generally the correlations are poor and the main determinant of POPs is age (Hue et al., 2007). It is hard to tell only on basis of associations which is the cause and which is the effect, or if both are caused by the same third factor. There is some evidence that the quality and not only quantity of food are involved. Less healthy food choices (Keski-Rahkonen et al., 2007) and increased meat consumption (Zazpe et al., 2011; Fogelholm et al., 2012) are associated with obesity. Obesity has been convincingly associated with type 2 diabetes (Ley et al., 2014); in fact in Finland nine of ten diabetics are overweight (BMI > 25, Pajunen et al., 2012). On the other hand, obesity has been associated with epigenetic transgenerational effects (Lind et al., 2016). One-generation delay could perhaps explain why the association is seen now although the concentrations of POPs were highest during 1970s and 1980s. If that is true, the effect should wane in near future.

We have previously published a case-control study on the association between soft tissue sarcoma and PCDD/Fs (polychlorinated dibenzo-*p*-dioxins and dibenzofurans) (Tuomisto et al., 2004). In this study, subcutaneous fat samples were collected from 954 patients with soft tissue sarcomas or controls undergoing appendicitis operation, and PCDD/Fs were analyzed. Patients also filled in a questionnaire asking a number of variables, including their dietary habits, weight history, and chemical exposure. This study material allows us to study in detail the influence of various factors on the concentrations of PCDD/Fs in fat.

The most obvious determinant of any congener concentration in the study was age (Tuomisto et al., 2004, 2005; Kiviranta et al., 2005), and in fact the concentrations were higher than expected in older age groups. This was interpreted as indicating carry-over from higher intake levels in the past (Tuomisto et al., 2004). Decreasing concentrations have in fact been clearly shown by actual measurements of PCDD/F and PCB levels in the population (Kiviranta et al., 1999; Lignell et al., 2009), as well as in various food items in Finland (Kiviranta et al., 2001) and in other countries (Liem et al., 2000). On this background, we have now modeled the kinetics of relevant PCDD/Fs using general laws of pharmacokinetics and compared the theoretical behavior of the compounds to measured values on population level and in some specific groups.

In short, we argue that causal conclusions on POPs and type 2 diabetes cannot be drawn until it is excluded that both of them might be caused by a same third factor, for example diet rich in red meat (Ley et al., 2014), or conversely, lack of fruit, vegetables, and other plant products in the diet, and until the pharmacokinetic properties of POPs are considered. In fact the pharmacokinetic considerations will be valid not only for diabetes, but for any health outcome associated with POPs.

2. Material and methods

2.1. Analysis of variables of the sarcoma study

A detailed description of sample collection and PCDD/F analysis has been given in the previous papers (Tuomisto et al., 2004; Kiviranta et al., 2005).

Briefly, sarcoma patients attended the University hospitals of Helsinki, Kuopio, Turku and Tampere. All patients over 15 years of age operated for soft tissue sarcoma between June 1997 and December 1999 were eligible as cases. Patients over 15 years of age and operated due to appendicitis in any study hospital from the same catchment area were eligible as controls. Informed consent was obtained from all patients in writing before the operation, and the study was duly approved by the ethics committees. The total number of patients recruited was 972, and after exclusion of some patients for technical reasons (e.g. too small sample, see Tuomisto et al., 2004), data on 954 patients (148 cases and 806 controls) were available. Because we did not find a significant difference in PCDD/F concentrations between the patients and controls, the disease status was ignored for the purposes of the present study.

A subcutaneous fat sample obtained during an appendectomy or sarcoma operation was analyzed for 17 PCDD/F congeners using gas chromatography–mass spectrometry (Vartiainen et al., 1997)