Levels of Polychlorinated Organic Compounds in Dutch mother's milk: Time trend analysis of dioxins by means of Physiologically Based Pharmaco Kinetic modelling.

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Introduction

In the Netherlands human milk is regularly analysed on the presence of organochlorine pesticides (OCPs, since 1972), polychlorinated biphenyls (PCBs, as individual compounds since 1983), and dibenzodioxins and dibenzofurans (PCDDs and PCDFs, since 1988)[1,2,3]. The main purpose of this five yearly monitoring program is to investigate the time-trend of polychlorinated organic compounds (POCs) and the identification of potential determinants of their levels in human milk. Since dietary intake represents the common route (>95%) of human exposure, the association with food intake is studied in particular.
This paper shortly reviews the time-trends of POCs in mother's milk as observed in the 1972, 1983, 1988 and the 1993 campaigns. Furthermore a method to analyse the time-trend of PCDDs and PCDFs with the aid of PBPK modelling is presented.

Methods

Sampling strategy

The research populations consisted of representative samples of Dutch mothers who recently gave birth to their babies. From 1993 onwards the research population was restricted to primiparae (mothers of first born children). The mothers (N varied between 100-400) were approached in co-operation with maternity centres scattered all over the Netherlands. The respondents were asked to collect a 100 ml breast milk sample between day 6 and day 10 after delivery and to fill out several questionnaires. The milk sample as well as the questionnaires were returned by post in a prepaid envelope and box which were placed at the mother's disposal.

Laboratory analyses

The analytical programme consisted of compound specific determinations of sixteen PCBs and seventeen 2,3,7,8-substituted PCDDs and PCDFs and ten OCPs. Details of these analytical methods have been described previously[4].

The PBPK model of dioxins and furans:

The PBPK model used is extensively described by Van der Molen et al.[5,6]. Basically the model assumes that the distribution of PCDDs and PCDFs in the body is determined by the lipid-fraction of the blood and the organs. Elimination is assumed to occur exclusively by the liver and, during lactation, via transfer from the blood to the lipid fraction of mother's milk. The intake of PCDDs

and PCDFs is assumed to occur exclusively from food. In 1991 the concentrations of PCDDs and PCDFs were determined in various food items. These concentration measurements were combined with data on the food consumption habits of the Dutch population in 1987. For each PCDD and PCDF congener this combination resulted in an estimate of the daily intake in ng/day of the congener in a cross-section of the Dutch population in 1991[7].
The PBPK model also incorporates a correction function for the historic development of the intake of PCDDs and PCDFs[5,6]. With this correction function, which is assumed to be the same for all congeners, the daily intake is scaled relative to its 1991 intake. For example, from 1920 onwards the daily intake of TCDD was assumed to increase to a peak intake in early 1960. At this time point the intake of TCDD was assumed to be almost three times higher than the intake in 1991. After 1960 the intake of TCDD was assumed to gradually decline to the level which was observed in 1991.

Output of PBPK model
For each congener the PBPK model simulates the amount of the congener as expected in mother's milk in a cross-section of the Dutch female population (individuals of 0-70 years of age) in 1993 and 1998. TEQ values of mother's milk were obtained by the summing up the products of the absolute amounts of PCDDs and PCDFs with their TEF factors[8].

Results
Laboratory analyses (up to 1993)
For the OCPs the levels in human milk show a downward trend in the period between 1972 and 1993. With the exception of HCB, β-HCH and p,p'-DDE the OCPs were in 1993 found at levels around the limits of determination. Unlike the time trend for OCPs no significant changes can be observed for PCB congeners (IUPAC nos. 118, 138, 153 and 180). In 1988 PCDDs and PCDFs were determined only in pooled samples, whereas in 1993 individual samples were available. When levels are expressed in toxic equivalents of 2,3,7,8-TCDD[8], the 1993 data show a decrease of approximately 30% compared with the average of 34 pg I-TEQ/g fat observed in the 1988 survey.

Determinants of contaminant levels
The main determinants of the POC levels in human milk which have been demonstrated by the surveys so far are: age and Body Mass Index of the mother, smoking by the mother, and food intake of the mother, especially the intake of fish, beef, meat products and milk (products)[3].

PBPK modelling.
Given the assumptions made with respect to the historical correction function, the PBPK model contains only one unknown parameter, i.e. the congener specific elimination constant of the liver. For each congener the value of this constant was obtained by fitting the PBPK model to the measured amounts of these compounds, in the 1993 human milk survey[6].
Fig 1 shows the result of this calibration procedure for the I-TEQ levels of the 1988 and the 1993 survey. It can be observed that the model underestimates the measured values of the 1988 campaign. Consequently, the decrease in I-TEQ between 1988 and 1993 may also be an underestimation. The scatter of measured values around the simulated curve reflects the substantial

variation due to inter-individual differences in body fat, elimination rates and (historical) intakes, which the PBPK model does not take into account yet..

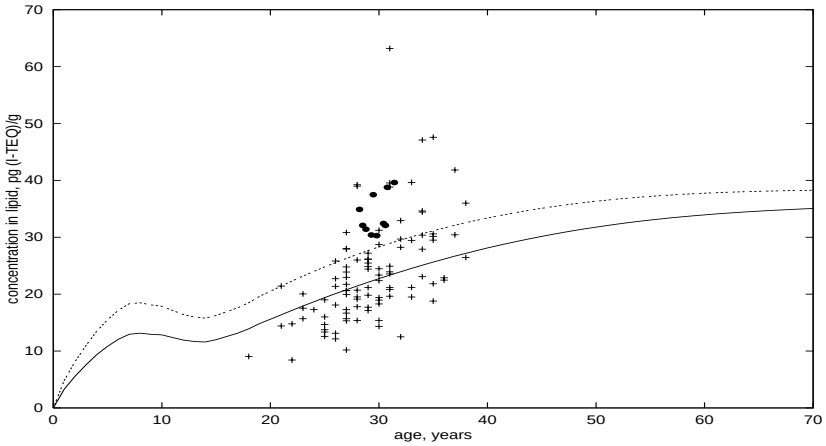

Figure 1:Simulations of the I-TEQ levels in human milk in 1993 (solid curve) and 1988 (dashed curve). The crosses represent the measured I-TEQ levels in human milk in 1993 (individual samples). The circles represent the measured I-TEQ levels in human milk in 1988 (pooled samples).

Figure 2 shows the results of the simulations for the expected total amount of dioxins and furans (expressed as I-TEQ) in mother's milk, for a cross section of the female population in 1998 (dashed curve). The 1993 simulations are presented as a reference (solid curve). To illustrate the difference between simulations of a cross section of the entire female population and simulations of individual birth cohorts, four curves of women aged 20, 25, 30 and 35 years in 1998, are presented in this figure too.

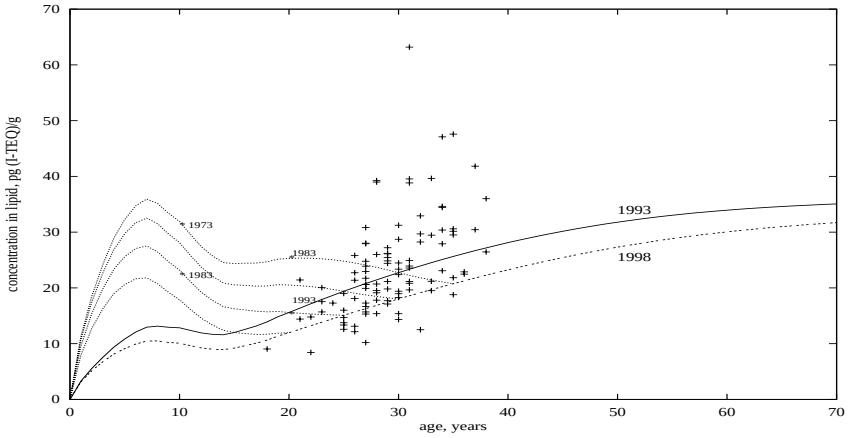

Figure 2:I-TEQ levels in milk by age for a measured cross-section in the female population in 1993 (crosses), and a simulated cross section in the female population in 1993 (solid curve), a simulated cross section in 1998 (dashed curve) and 4 simulated birth cohorts of women who will be 20, 25, 30 and 35 years old in 1998.

In figure 2 it can be seen that the amounts of PCDD and PCDFs in mother's milk are expected to decrease in the period between 1993 and 1998. Table 1 quantifies this decrease. PCDD and PCDF levels are expected to further decline with 20 to 30% in the period between 1993 and 1998.

Table 1: PBPK Simulated I-TEQ values of mother's milk for women aged 20, 25, 30 and 35 years in 1993 and in 1998.

age in years	I-TEQ, 1993	I-TEQ, 1998	Ratio I-TEQ '98/'93
20	15.6	12.0	0.77
25	19.4	15.1	0.78
30	22.7	18.0	0.79
35	25.6	20.8	0.81

Discussion

From 1970 onward the levels of POCs in human milk are, except for PCBs, declining in the Netherlands. This is consistent with the reported decline of their levels in food[7,9]. Both trends illustrate the effects of regulatory measures which have been taken to reduce the emission and/or use of these compounds. In 1998 the most recent sampling campaign of the Dutch human milk study was carried out. Just now the data of the current POC levels are not yet available. By use of the PBPK model the estimated 1998 levels are expected to be about 20-30% lower than the 1993 levels. During the conference the (preliminary) results of the 1998 survey will be discussed with respect to the 1998 levels predicted by the PBPK model.

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