DIOXIN LEVELS IN DUTCH HUMAN MILK: A 50% DECREASE IN 10 YEARS. HOW WILL FUTURE TRENDS DEVELOP?

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Introduction

Since the beginning of the nineties the dioxin emissions levels have been successfully (about 90%) reduced in the Netherlands (1). Consequently, decreased levels in food and in human milk have been demonstrated (2-4). However, the recent incidents: 'contamination of citrus pulp', 'dioxins in Belgian chickens' point out uncontrolled links in the food chain and illustrate the necessity of continuous monitoring activities. Furthermore, in 1998 a WHO Consultation recommended to lower the (health based) TDI for dioxin and related compounds from 10 to a range of 1-4 pg TEQ/kg body weight (5). Because current intakes are on average still within the proposed TDI range it is important to know whether or not the downward trend in the occurrence in foods and human milk will proceed. In this paper the temporal trend in the occurrence of dioxins in human milk will be presented for the period 1988–1998. The occurrence data presented have been used to predict the time course of dioxin levels, in particular 2,3,7,8-TCDD, in human milk in the forthcoming period by use of a Physiologically Based Pharmaco Kinetic (PBPK) model. Here we present the results of our

Methods

Sampling strategy

Since 1988, the level of dioxins are measured in Dutch human milk at five years intervals. The most recent sampling campaign has been carried out in 1998. The research population consisted of a representative sample of about 300 Dutch mothers (primiparae), who have given birth to their first baby in September/October 1998. The mothers were approached in co-operation with 26 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. In addition, they were asked to fill out an extensive food frequency questionnaire (6) and a questionnaire on personal characteristics and habits, characteristics of pregnancy and delivery, and characteristics of the child. The milk samples as well as the questionnaires have been returned by post in a prepaid envelope and a 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 three OCPs (HCB, β-HCH, p-p-DDE). Details of these analytical methods have been described in detail elsewhere (2).

PBPK modelling of dioxins and furans

The PBPK model used to describe the excretion of PCDDs and PCDFs in mother's milk basically assumes that the distribution of these compounds in the human body is determined by the neutral lipid-based fraction of blood and of the organs. So, binding to proteins in the organs is neglected[7,8]. Elimination is assumed to occur by metabolism exclusively in the liver and by lactation. During lactation transfer of PCDDs and PCDFs from the blood to the neutral lipid fraction of mother's milk occurs. The intake of dioxins and furans was assumed to occur exclusively from food. This intake was calculated as follows. First, the intake of PCDDs and PCDFs (ng/day) as determined in a cross-section of the Dutch population in 1991[9] was taken. This intake alone however does not suffice to describe the toxicokinetics of PCDFs and PCDDs in humans. For, the historic and future exposure of humans to PCDFs and PCDDs may differ

significantly from the intake in 1991[9,10]. To obtain the historic and future exposure to PCDFs and PCDDs the 1991 intake was therefore corrected by means of a congener specific correction function. This correction function is as follows. Based on sedimentation results of PCDFs and PCDDs[10,11] the exposure to TCDD was assumed to increase form a natural background level in the period between 1920 and 1940 to a peak exposure level in 1960. This peak exposure equals 17 times the natural background level[11]. In concordance with observations of the time-trend of PCDDs and PCDFs in Dutch duplicate diet studies[9,10] the intake of TCDD was assumed to gradually decline from 1960. The rate of this decline, as well as the maximum exposure in 1960, were obtained from the mentioned time-trend. Given this time-trend the correction function predicts that the exposure to TCDD will reach the natural background again around 2010.

Output of PBPK model
For each congener the PBPK model simulates the time-course of the concentration of the congener in the blood, the organs and mother's milk in yearly cohorts of Dutch women born. Based on these simulations the concentration of the congener as expected in mother's milk of primiparae in a cross-section of the Dutch female population (individuals of 0-40 years of age) in 1993, 1998, 2003 and 2008 were calculated.

Results
Population
The 1998 data in this paper are based on the (preliminary) analyses of 36 human milk samples.

Table 1: Population characteristics of 36 woman of the 1998 cohort.

Characteristic	N	Mean ± sd	Lowest	Median	Highest
Age	35	28,9 ± 3,0	22	30	34
BMI: Prenatal	36	22,8 ± 2,3	17,8	22,7	30,1
Postnatal	32	24,6 ± 2,8	18,3	24,4	31,1
Smoking: yes	14				
no	22				
Alcohol: yes[1]	25				
no	11				

[1] *before pregnancy*

Laboratory analyses
Table 2. One decade I-TEQ (pg/g fat) levels in human milk in the Netherlands.

Year	N	Lowest	Median	mean	±SD	highest
1988	10[2]	30.6	32.7	34.2	3.4	39.6
1993	103[3]	8.4	21.7	23.5	8.9	63.1
1998	36[3]	9.2	17.0	17.1	5.8	33.0

[2] *pooled samples*
[3] *individual samples*

The data in table 2 show a 50% decrease in mean I-TEQ level between 1988 and 1998.

PBPK modelling: TCDD.
Given the correction function for the historic and future development of the intake of TCDD the PBPK model contains only one unknown parameter, i.e. the (congener specific) elimination constant of the liver. The value of this constant was obtained by fitting the PBPK model to the measured concentrations of TCDD in the 1993 human milk campaign (model calibration). The calibrated model was used to simulate the concentration of TCDD in mother's milk of primiparae as expected in 1998, 2003 and 2008. The simulated 1998 concentrations were compared with the actually measured 1998 TCDD concentrations (model verification). Fig 1 shows the result of the

model calibration and model verification procedure. As shown the calibration procedure resulted in a reasonable description of the (mean) concentration of TCDD present in mother's milk in the 1993 and 1998 campaigns. These simulations indicate a steady decline of the concentration of TCDD over time. For example, Fig. 1 shows that the concentration of TCDD in milk fat of primiparae aged 24 years was estimated to be 2.8, 1.9, 1.7 and 1.6 pg TCDD/g milk fat in 1993, 1998, 2003 and 2008 respectively. It can also be noticed that the decrease of TCDD in milk fat flattens out. This effect is further illustrated in Fig. 2 which shows the concentration of TCDD in milk fat of primiparae aged 24 years in the period between 1974 and 1993 and aged 30 in the period between 2000 and 2020. In concordance with the result shown in Fig. 1 a sharp decline of this concentration is expected in the period between 1974 and 1993. Thereafter the concentration of TCDD in mother's milk is expected to decline much slower. In the period between 2010 and 2020 a more or less constant TCDD level is expected to be reached in Dutch mother's milk. This effect is caused by the exposure of TCDD which has returned to near natural background levels in the period after 2000.

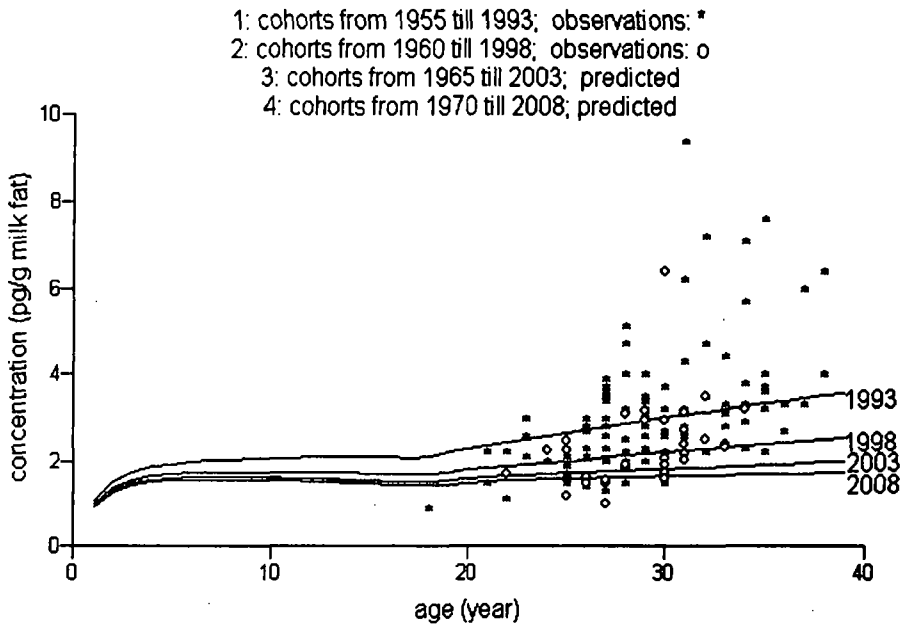

Figure 1 Simulation of the concentration of TCDD in milk fat of Dutch primiparae in 1993, 1988, 2003 and 2008. The asterisks (1993, N=91) and open circles (1998, N=32) represent the measured concentrations of TCDD in human milk in 1993 and 1998 (individual samples).

Conclusions

The data in this paper show that the I-TEQ concentration of PCDDs and PCDFs in Dutch human milk has been halved in the period between 1988 and 1998, illustrating the effectiveness of measures which have been taken in the past to decrease the accumulation of PCDDs and PCDFs in the food chain and, consequently, the human body. When PBPK modelling was used to extrapolate this trend beyond the mentioned time period for TCDD a further decrease is expected to occur in the period between 1998 and 2010. In the epriod between 2010 and 2020 the concentration of TCDD is expected to become more or less constant.

The PBPK analysis presented in this paper is currently being extended to congeners other than TCDD as well. These results as well as a comparison of the Dutch time-trend with dioxin trends in human milk in other countries will be presented.

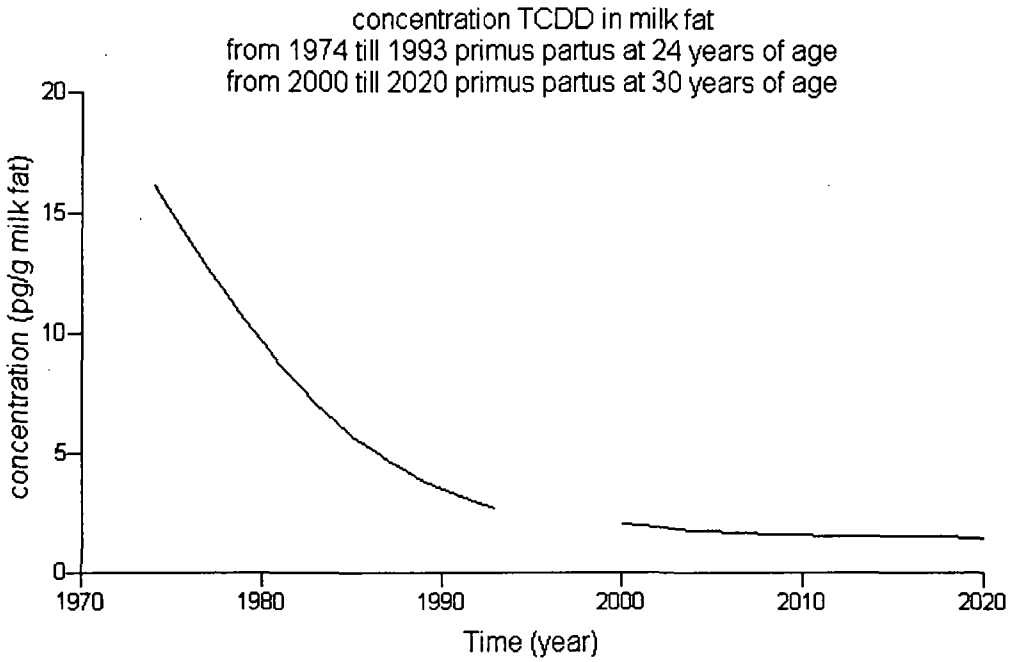

Figure 2 Simulation of the time-trend of the concentration of TCDD in milk fat of Dutch primiparae in the period between 1974 and 2020. In the Netherlands the age of primiparae has changed in the early seventies from around 24 years to around 30 years. For this reason an age of 24 years was assumed to represent the age for primiparae born in the period up to 1970. Similarly, for primiparae born in for the period beyond 1970 this age was set at 30 years.

References

1. Cuijpers C.E.J., H.J. Bremmer, N.B. Lucas Luijckx, J.A. van Zorge and A.K.D. Liem. *Organohalogen Compounds* **1998**; 38, 59-64.
2. Liem A.K.D., J.M.C. Albers, R.A. Baumann, A.C. van Beuzekom, R.S. den Hartog, R. Hoogerbrugge, A.P.J.M. de Jong and J.A. Marsman. *Organohalogen Compounds* **1995**, 26, 69-74.
3. Albers J.M.C., I.A. Kreis, A.K.D. Liem and P. van Zoonen. *Arch Environ Contam Toxicol* **1996**, 30, 285-291
4. Liem A.K.D., R. Hoogerbrugge, C.E.J Cuijpers, R.S. den Hartog, W.C. Hijman, S.H.M.A. Linders, J.A. Marsman, E. G. van der Velde and B. Zomer. *Organohalogen Compounds* **1997**, 33, 112-115.
5. Van Leeuwen F.X., M. Younes. *Organohalogen Compounds* **1998**, 8, 295-298.
6. Van Dooren-Flipsen M.M.H., J.D. van Klaveren. **1998**, RIKILT-DLO report number: 98.004 (in Dutch).
7. Zeilmaker, M.J. and J.C.H. van Eijkeren. *RIVM report 601503.010* **1998**.
8. Zeilmaker, M.J., Fiolet, D.C.M. and C.E.J. Cuypers. *RIVM report 529102.010* **1999**.
9. Liem A.K.D. and R.M.C. Theelen. *(Thesis),* Dioxins: Chemical Analysis, Exposure and Risk Assessment. *(chapter 5*) Utrecht University, **1997**, ISBN 90-393-2012-8.
10. Molen, G.W.van. *(Thesis)*, A physiologically based mathematical model for the long-term kinetics of dioxins and furans in humans. Free University Amsterdam, **1998**, ISBN 90-9011844-6.
11. Päpke, O. Environmental Health Perspectives **1998**, 106, 273-731.