Health Risk Assessment for Newborns Exposed to Organochlorine Compounds Through Breast Feeding

Ayotte, P.[A], Carrier, G.[B], Dewailly, É.

[A] Département de Médecine sociale et préventive, Faculté de Médecine, Université Laval, Ste-Foy, Qc., Canada G1K 7P4
[B] Département de Médecine du travail et d'Hygiène du milieu, Faculté de Médecine, Université de Montréal, Montréal, Qc., Canada H3C 3J7

Introduction

The Inuit population living in Nunavik (Arctic Québec) is exposed to various xenobiotics through their country foods. Results of 105 breast milk analysis conducted in 1989-1990 showed a mean PCB (Aroclor 1260) concentration of 2.9 mg/kg lipids, a level five-fold greater than that measured in breast milk samples of women living in the southern part of the province (0.52 mg/kg lipids)[1]. Mean concentrations of chlorinated pesticides or their metabolites (DDE, dieldrin, hexachlorobenzene, mirex) in milk samples from Inuit women were between three to five times greater than those of the reference population[2]. Differences between the two groups were less important for PCDDs and PCDFs levels[1].

Calculated average daily intakes of most organochlorine contaminants found in breast milk exceed acceptable daily intakes. For example, assuming a 120 ml/kg body weight (BW) daily intake of milk, the calculated intake of dioxin-like compounds is 226 pg TEQ/kg/day, 2260 times greater than the reference dose proposed by the US Environmental Protection Agency in 1987[3]. However, one cannot conclude from this crude preliminary risk assessment that exposure to contaminants found in breast milk poses a significant health risk for the newborns of this Inuit population. First, exposure through breast feeding occurs at a period of rapid body growth. This limits the rise of body concentration because the increase in body burden due to breast feeding is opposed by an expanding volume of distribution[4]. Second, reference doses are established for chronic exposure, including in most cases exposure during a major part of the total lifetime. Considering the apparent benefits of breast feeding for the infant's health, which results in decreased postneonatal mortality[5], a more elaborate risk assessment must be conducted before issuing public health recommendations regarding breast-feeding practices.

In order to refine the health risk analysis, one approach is to better characterize the exposure by modeling the contaminant body burden through time using toxicokinetic models. A physiologically-based toxicokinetic model (PB/TK) for 2,3,7,8-TCDD-like compounds is available, which takes into account the non-linear relation between liver concentration and whole body concentration, which in turns impacts on the elimination rate[6),7]. Results are compared to body burden values associated with adverse health effects in animals to estimate the risk for the Inuit newborns.

Methods

The physiologically-based toxicokinetic (PB/TK) model developed for dioxin-like compounds takes into account the non linear elimination kinetics of these compounds observed in various species[6]. This is the result of liver enzyme induction triggered by the binding of dioxin-like compounds to the Ah receptor. The increase synthesis of cytochrome P450IA2, which displays a strong affinity for 2,3,7,8-TCDD, is apparently responsible for the increase capacity of the liver to sequester dioxin-like substances which is observed as body burden increases. In the model, this phenomenon is saturable and is described mathematically by a modified Michaelis-Menten equation developed for receptor-driven biological effects. The whole set of mathematical equation in the model is presented in detail elsewhere (Carrier et al., manuscript submitted for publication). This model was successful in depicting the temporal variation of TEQ body burden for Yusho and Yu-Cheng subjects exposed to various PCDF congeners (Carrier et al., manuscript submitted for publication).

Using this model and the total 2,3,7,8-TCDD TEQ concentration in milk fat, we estimated the concentration of dioxin-like compounds in the liver, the adipose tissues and in the whole body of the newborn at different time during breast-feeding and throughout lifetime. Concentrations of non-ortho coplanar PCB congeners (IUPAC nos. 77, 126 and 169), 2,3,7,8-polychlorodibenzo-p-dioxins and 2,3,7,8-polychlorodibenzofurans were multiplied by toxic equivalency factors (TEF) and summed to obtain the total 2,3,7,8-TCDD TEQ concentration[8]. Liver weight was set at 3.5% of total body weight. The maximal fraction of body burden in liver (f_{hmax}) was 0.72 and the apparent dissociation constant (K_{diss}) was 400 ng TEQ/kg. Birth weight was 3.32 kg for females and 3.55 kg for males.

Milk consumption at different ages was modeled according to data from ICRP[9]. Milk fat concentration was set at 3.5%. Milk fat concentration of dioxin-like compounds was assumed to be constant throughout the breast-feeding period. This leads to an overestimation of the dose received during breast-feeding, since milk secretion is an efficient route of elimination for organochlorines. We assumed that 85% of dioxin-like compounds in milk were absorbed and a 50% absorption from solid foods. Post-weaning doses were adjusted in order to take into account the greater food consumption per body weight in infants. From weaning to age 3, the dose from the diet was set at 10 pg/kg, 6 pg/kg from age 3 to 6 years, 5 pg/kg from age 6 to 14 years, 4 pg/kg from age 14 to 20 years and 3 pg/kg from age 20 to 75 years.

Separate simulations were conducted for males and females. Age- and sex-specific mean values for body weight and adipose tissue weight were obtained from the literature for general caucasian populations[10),11),12)]. For each sex, a median case was simulated using the median duration of breast feeding and the median concentration of dioxin-like compounds in breast milk. We also performed simulations for two cases: the newborn breast fed for the longest period and the newborn for which breast feeding duration was minimal.

Results

Results for the adipose tissue compartment are presented in figures 1 and 2 for females and males, respectively. In females (figure 1), simulations were performed for 1) median exposure (median breast-feeding duration: 51 weeks; median breast-milk concentration: 48 ng TEQ/kg lipids); 2) maximal exposure, corresponding to the maximal breast-feeding period (58 weeks; concentration in milk fat: 108 ng TEQ/kg) and 3) minimal exposure, i.e. breast-fed

for the shortest period (4.4 weeks; concentration in milk fat: 46 ng TEQ/kg). For comparative purposes, a typical southern Québec exposure is also presented (breast-feeding: 6 months; concentration of dioxin-like compounds in milk fat: 23 ng TEQ/kg).

For the maximal case, the adipose tissue concentration reached 264 ng TEQ/kg at the end of the breast feeding period and declined slowly thereafter to reach the concentration dictated by the mean exposure dose from food ingestion. The maximal concentration obtained for the median case was 125 ng TEQ/kg. For the minimal case, exposure through breast-feeding did not result in a noticeable peak and concentrations are slowly rising throughout lifetime. For all three cases, the concentrations reached during adulthood are similar. This is because a single set of exposure doses was used to take into account exposure resulting from ingestion of solid foods which is taking place following breast-feeding. In fact, theses doses will vary from one individual to another; amongst the 30 mothers for which data were available, the median concentration in breast-milk was 46 ng TEQ/kg lipids, varying form 19 to 114 ng TEQ/kg.

In males (figure 2), the median case was breast fed during 54 weeks (milk fat concentration: 43 ng TEQ/kg), the minimum case was weaned after 9 weeks (concentration in milk fat: 31 ng TEQ/kg) and the maximum case was exposed through breast-feeding during 60 weeks (milk fat concentration: 65 ng TEQ/kg). Results were similar to that of the females. Peak levels were lower at the end of the breast feeding period due to lower milk content for the corresponding mothers. Concentrations reached during adulthood are greater than those for females, due to a greater food intake per kg body weight and a smaller adipose tissue compartment than that of women.

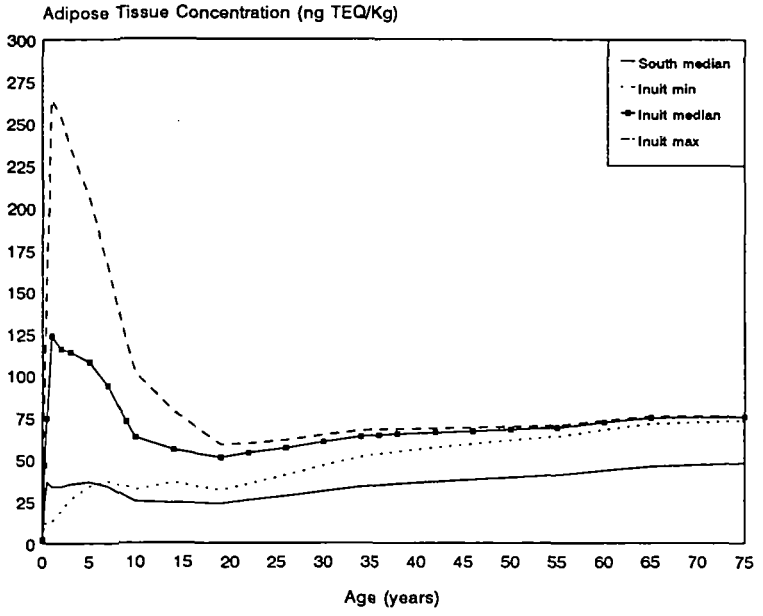

Figure 1: Adipose tissue concentration of dioxin-like compounds from birth to age 75 years in Inuit female (minimum, median and maximum exposure from breast-feeding) and southern Québec female (median exposure)

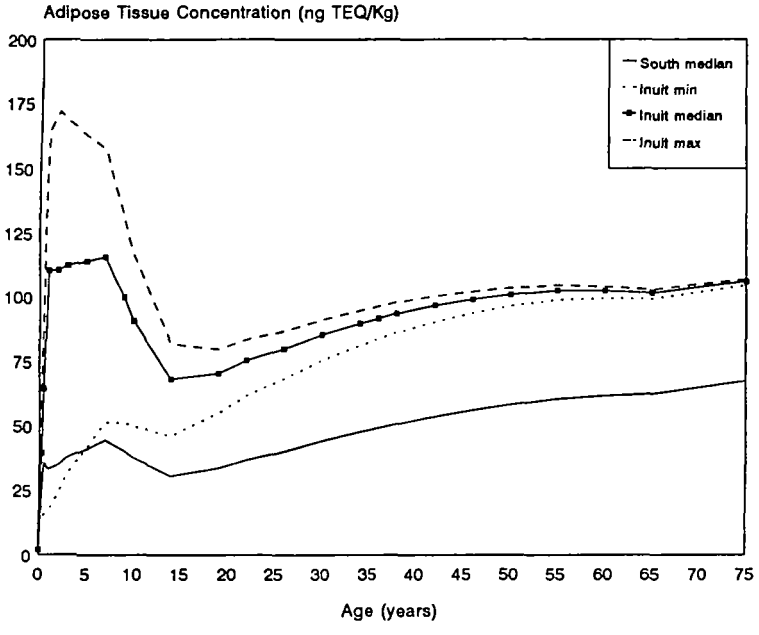

Figure 2: Adipose tissue concentration of dioxin-like compounds from birth to age 75 years in Inuit male (minimum, median and maximum exposure from breast-feeding) and southern Québec male (median exposure)

Discussion and conclusion

Two studies have been used to establish the no-adverse-effect level (NOAEL) for 2,3,7,8-TCDD. Results of a cancer bioassay conducted by Kociba et al.[13] pointed out to a no-observed-adverse-effect level (NOAEL) of 1 ng/kg/day in rats. The corresponding mean concentration measured in both liver and adipose tissue samples collected at the end of the study was 540 ng/kg. In a multigeneration reproduction study with rats exposed to 2,3,7,8-TCDD, the 1 ng/kg/day dose level was again identified as a NOAEL[14].

Assuming a similar concentration/response relationship in humans, even in extreme cases, where both the milk concentration is elevated and the breast-feeding duration is long, the NOAEL would not be exceeded, as depicted in figure 1 for a newborn female which was breast-fed during 58 weeks with a milk containing 108 ng/kg lipids. The maximal concentration predicted in adipose tissue, 264 ng/kg, is reached at the end of the breast-feeding period. This concentration is lower than that associated with the NOAEL (reproductive effects) by a factor of 2. The maximal liver concentration is estimated at 225 ng/kg (data not shown), a value also inferior by a factor of 2 to the liver concentration associated with the NOAEL (liver cancer). Furthermore, following weaning, levels will decrease to reach by age 20-30 years the mean body concentration expected from their exposure through the diet.

Recently, Mably et al.[15] reported adverse effects on the reproductive function of adult male rats induced by *in utero* and lactational exposure to 2,3,7,8-TCDD. Exposure of mothers to this compound was through a single dose at day 15 of gestation. A 64-ng/kg dose was

sufficient to depress by 40% the sperm content of cauda epididymis compared to controls. Assuming 1) that this effect is a function of the mother adipose tissue concentration; 2) instantaneous distribution to major storage sites (adipose tissues and liver) and 3) a similar susceptibility in rats and in humans, we may wish to characterize this risk. According to the toxicokinetic model, the 64 ng/kg body burden resulting from TCDD administration to pregnant rats in Mably et al. experiments would be associated with a 525-ng/kg concentration in adipose tissues. The highest concentration in milk lipids among the 30 Inuit women was 114 ng TEQ/kg. This concentration is lower than the LOAEL by a factor of 4.6, leaving a small margin of security, considering that adverse effects were induced at this dose and that humans may be more susceptible to these effects than rats.

Even more recently, increased incidence of endometriosis has been reported in rhesus monkeys exposed during 4 years to a diet containing 5 ppt and 25 ppt of 2,3,7,8-TCDD, compared to control animals receiving a normal diet[16]. In the 5-ppt group, 2,3,7,8-TCDD adipose tissue concentration reached approximately 100 ng/kg near the end of the treatment period and fell to approximately 50 ng/kg at 18 months post-treatment[17]. From results presented in figure 1, a typical Inuit woman receiving the median exposure through breast-feeding would show a 125 ng/kg fat concentration at weaning, gradually declining thereafter to reach a concentration exceeding 50 ng/kg at adulthood, assuming that the woman adopts the typical traditional diet comprising large amounts of fatty tissues from sea mammals. Hence, it is likely that a substantial proportion of Inuit women would have, during most of their lifetime, adipose tissue concentrations close to or higher than those associated with increased incidence of endometriosis in rhesus monkeys.

In conclusion, according to computer simulations effected to model the variation of dioxin-like compounds concentrations in Inuit newborns during breast-feeding and throughout adulthood, the maximal concentrations are below those associated to the NOAEL for cancer in rats. However, predicted concentrations in adult Inuit women are similar to those associated with adverse effects on reproduction in male rats and in female rhesus monkeys.

Acknowledgments

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