

Effects of Pre- and Postnatal Exposure to Chlorinated Dioxins and Furans on Human Neonatal Thyroid Hormone Concentrations

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Animal studies have shown that dioxins influence plasma thyroid hormone concentrations. To investigate the effect of chlorinated dioxins and furans on thyroid hormone concentrations in humans, we studied 38 healthy breast-fed infants. The study population was divided into two groups according to the dioxin concentrations in milk fat of their mothers. Blood samples were taken at birth and at the ages of 1 and 11 weeks. At birth a tendency to higher total thyroxine (tT₄) concentrations was found in the high exposure group. At the ages of 1 and 11 weeks the increase of mean tT₄ concentrations and tT₄/thyroxine-binding globulin ratios in the high exposure group reached significance as compared to the low exposure group. At birth and 1 week after birth, mean thyrotropin (TSH) concentrations were similar in both groups, but at the age of 11 weeks the mean TSH concentrations were significantly higher in the high exposure group. We postulate that the observed plasma tT₄ elevation in infants exposed to dioxins before and after birth is the result of an effect on the thyroid hormone regulatory system. *Key words:* breast milk, dibenzofurans, dioxins, prenatal exposure, thyroid gland, thyroid hormones, xenobiotics. *Environ Health Perspect* 101:504–508(1993)

Chlorinated dioxins and dibenzofurans, henceforward jointly referred to as dioxins, are highly toxic tricyclic aromatic compounds, among others formed as by-products in the manufacture of herbicides and during combustion of municipal and industrial wastes (1,2). Rather high concentrations of these lipophilic compounds have been detected in human milk, especially in the Netherlands, Belgium, and the United Kingdom (3). This contamination of breast milk is a reflection of exposure of humans to these compounds, mainly by food. Meat, dairy products, and fish oils are the main sources (4–6). Infants may be exposed to high levels of these compounds via breast-feeding. Fetuses can also be exposed to dioxins because these xenobiotics pass through the placental barrier (7).

Several animal studies have shown that dioxins can influence plasma thyroid hormone concentrations. Increased (8,9) and decreased (8,10–15) thyroxine concentra-

tions have been described after administration of 2,3,7,8-tetrachloro-*p*-dibenzodioxin (2,3,7,8-TCDD), the most toxic dioxin. Polychlorinated biphenyls (PCBs) have the same effects on thyroid hormone concentrations (16). As an altered thyroid hormone status in the newborn may influence the maturation of the central nervous system and have consequences for psychomotor development (17), we began a study to investigate thyroid hormone concentrations in relation to dioxin concentrations in breast milk in a population of breast-fed infants.

Subjects

In the period June 1990–May 1991, 38 healthy, pregnant, Caucasian women gave informed consent for us to study the effects of pre- and postnatal exposure to dioxins in their offspring, according to a protocol approved by the medical ethical committees of the Academic Medical Centre and Hospital De Heel. Of the 38 infants, 35 were born in the delivery room of the local hospital; 3 were born at home under supervision of a midwife.

The mothers were between the ages of 21 and 38 years (mean 29.0 years) and had uneventful pregnancies without the use of antithyrotic drugs or iodine-containing compounds. None of them had a family history of thyroid disease. All intended to breast feed for at least 12 weeks; however, in 11 women breast-feeding ceased 4 to 11 weeks after delivery. The infants were all full-term, healthy babies with birth weights above 2500 g.

Methods

Maternal venous blood samples were taken just before or just after delivery. Immediately after birth, cord blood was sampled. Blood samples were taken from the infants at ages 1 and 11 weeks by venipuncture, shortly after feeding. All blood samples were centrifuged within a few hours after sampling, and the plasma was kept frozen at -20°C until analysis was performed.

In all plasma samples, we measured total 3,3',5,5'-tetraiodo-L-thyronine (tT₄) and thyroxine-binding globulin (TBG) concentrations. Additionally, concentra-

tions of thyrotropin (TSH) were determined in cord blood and in the surplus of plasma taken 1 and 11 weeks after birth (25, 26, and 30 samples, respectively). In the remaining plasma of 25 cord blood samples, we measured the concentrations of total 3,5,3'-triiodothyronine (tT₃), free T₄ (fT₄), and 3,3',5'-triiodothyronine (reverse T₃, rT₃). In 26 plasma samples taken at the age of 11 weeks, tT₃ concentrations were measured.

At the ages of 1 and 11 weeks urine samples were collected to control for iodine excretion. Samples were frozen at -20°C until analysis was performed.

Three weeks after delivery, two milk samples were collected from each mother. While the infant was suckling one breast, the milk sample was taken from the other breast with an electrical breast pump. The breast was emptied as much as possible. Each mother collected two milk samples during 1 day, which were mixed thoroughly, pooled, and frozen at -20°C until analysis of dioxins was performed.

We measured concentrations of the 17 most toxic congeners (7 dioxins and 10 dibenzofurans). The concentration of each congener was multiplied by its toxicity equivalency factor (TEF), which is the relative toxicity with regard to 2,3,7,8-TCDD, the most toxic congener (18). By summing these products, we calculated the toxicity of a mixture and expressed it as toxic equivalence (TEQ). In this study chlorinated dioxin and dibenzofuran concentrations (summarized as dioxin concentrations) are expressed in ng TEQ/kg milk fat.

At the end of the study, we calculated the median dioxin concentration in milk fat. The mother–infant couples with a dioxin concentration below the median were assigned to the low exposure group. The others were assigned to the high exposure group. We compared the measured items between the low and high exposure groups. Control groups were not available because in Western Europe all individuals are more or less exposed to dioxins. The use of bottle-fed infants as controls was considered inappropriate for three reasons. First, because of the different social backgrounds between women who decide to breast feed and those who decide to bottle feed, it is not possible to randomize between breast-feeding and bottle-feeding. Second, when bottle feeding is started from the first day of birth, no representative

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breast-milk samples can be taken to estimate prenatal exposure. Third, the prolonged effects of intrauterine exposure cannot be excluded, and fourth, T_4 and T_3 concentrations are higher in breast-fed infants compared to bottle-fed infants (19).

Analytical Methods

After freeze drying, the sample was spiked with 17 ^{13}C -labeled dioxins and dibenzofurans. The sample was then Soxhlet-extracted with toluene for 24 hr. After evaporating the toluene, the extracted lipids were determined gravimetrically. Blank and reference samples (cow's milk) were run on a regular basis. Thereafter, a two-step "clean-up" was done using an activated carbon column followed by two columns filled with $AgNO_3$ on silica gel and Al_2O_3 , respectively (20). After concentrating the sample, we quantified it using gas chromatography and mass spectrometry (HP 5970 GC, Kratos Concept MS). We used a mixture of ^{13}C -labeled dioxins and dibenzofurans as an internal standard. Blank controls were included. Quality of measurements is under control of international round-robin studies.

Plasma concentrations of tT_4 , tT_3 , and rT_3 were determined using radioimmunoassay according to Chopra (21), Larsen (22), and Wiersinga (23), respectively. Concentrations of TBG and FT_4 fractions were determined using radioimmunoassay diagnostic kits (Eiken Chemical Co and Byk-Sangtec Diagnostica, respectively). We determined TSH concentrations using an immunoradiometric assay kit (Immunotech International). Plasma samples taken 1 and 11 weeks after birth were diluted 10 times before measuring TSH concentrations. Iodine concentrations in urine were measured according to De Vijlder et al. (24).

We used the two-tailed, independent Student's t -test to test the significance of differences in measured items between the low and the high exposure group.

Results

Five cord blood samples and nine maternal blood samples were not available for analysis due to problems with procedures in the beginning of the study (one and four cord blood samples and four and five maternal samples in the low and high exposure groups, respectively). From the samples taken 11 weeks after birth, 4 were lost due to technical errors (1 and 3 in the low and high exposure groups, respectively); the lost sample in the low exposure group belonged to a child that had been switched to bottle-feeding already; the 3 samples lost in the high exposure group were from completely breast-fed infants. Eleven mothers prematurely ended breast-feeding

Table 1. Concentrations of measured congeners in the low and high exposure groups (ng/kg milk fat)

	TEF	Mean \pm SEM		p^a
		Low exposure	High exposure	
2,3,7,8-TCDD	1	2.82 \pm 0.30	4.39 \pm 0.58	0.023
1,2,3,7,8-PeCDD	0.5	5.73 \pm 0.54	15.17 \pm 1.70	<0.001
1,2,3,4,7,8-HxCDD	0.1	1.05 \pm 0.47	1.30 \pm 1.10	0.839
1,2,3,6,7,8-HxCDD	0.1	32.67 \pm 2.24	64.72 \pm 5.17	<0.001
1,2,3,7,8,9-HxCDD	0.1	4.00 \pm 0.30	8.76 \pm 2.24	0.049
1,2,3,4,6,7,8-HpCDD	0.01	47.25 \pm 6.75	59.13 \pm 7.87	0.260
OCDD	0.001	272.08 \pm 27.70	314.18 \pm 36.03	0.361
2,3,7,8-TCDF	0.1	2.03 \pm 1.30	1.76 \pm 0.87	0.863
1,2,3,7,8-PeCDF	0.1	0.03 \pm 0.02	0.24 \pm 0.24	0.384
2,3,4,7,8-PeCDF	0.5	14.29 \pm 1.04	29.46 \pm 2.31	<0.001
1,2,3,4,7,8-HxCDF	0.1	4.21 \pm 0.31	9.59 \pm 1.11	<0.001
1,2,3,6,7,8-HxCDF	0.1	4.20 \pm 0.36	8.01 \pm 0.80	<0.001
1,2,3,7,8,9-HxCDF	0.1	1.82 \pm 0.20	4.40 \pm 0.75	0.003
2,3,4,6,7,8-HxCDF	0.1	BDL	BDL	
1,2,3,4,6,7,8-HpCDF	0.01	4.76 \pm 0.60	7.01 \pm 1.05	0.071
1,2,3,4,7,8,9-HpCDF	0.01	BDL	BDL	
OCDF	0.001	0.37 \pm 0.11	1.99 \pm 0.76	0.048

TEF, toxicity equivalency factor; BDL, below detection limit.

^aTwo-tailed, independent Student's t -test.

Table 2. Thyroid hormone and TSH concentrations compared between low and high exposure groups in cord blood

	Low exposure		High exposure		p^a
	Mean \pm SEM	<i>N</i>	Mean \pm SEM	<i>N</i>	
tT_4 (nmol/l)	122.5 \pm 4.1	18	134.3 \pm 4.8	15	0.071
TBG (nmol/l)	520.1 \pm 27.2	18	589.5 \pm 30.5	15	0.099
tT_4 /TBG	0.240 \pm 0.007	18	0.232 \pm 0.008	15	0.45
TSH (mU/l)	10.4 \pm 1.3	14	11.9 \pm 1.9	11	0.58
tT_3 (nmol/l)	1.22 \pm 0.20	14	1.01 \pm 0.07	11	0.34
fT_4 (pmol/l)	13.8 \pm 0.4	14	14.8 \pm 0.4	11	0.12
rT_3 (nmol/l)	2.33 \pm 0.31	14	2.51 \pm 0.16	11	0.61
tT_3 / tT_4	0.010 \pm 0.001	14	0.008 \pm 0.001	11	0.16
rT_3 / tT_3	2.54 \pm 0.48	14	2.58 \pm 0.22	11	0.94

tT_4 , total 3,3',5,5'-tetraiodo-L-thyronine; TBG, thyroxine-binding globulin; TSH, thyrotropin; tT_3 , 3,5,5'-triiodothyronine; fT_4 , free 3,3',5,5'-tetraiodo-L-thyronine; rT_3 , reverse T_3 .

^aTwo-tailed, independent Student's t -test.

Table 3. Thyroid hormone and TSH concentrations compared between low and high exposure groups at the age of 1 week

	Low exposure		High exposure		p^a
	Mean \pm SEM	<i>N</i>	Mean \pm SEM	<i>N</i>	
tT_4 (nmol/L)	154.5 \pm 6.3	19	178.7 \pm 5.5	19	0.006
TBG (nmol/L)	532.6 \pm 16.3	19	546.2 \pm 19.1	19	0.59
tT_4 /TBG	0.291 \pm 0.009	19	0.332 \pm 0.011	19	0.006
TSH (mU/L)	2.93 \pm 0.41	15	2.56 \pm 0.41	11	0.51
Iodide excretion ^b	921 \pm 98	18	879 \pm 181	16	0.84

tT_4 , total 3,3',5,5'-tetraiodo-L-thyronine; TBG, thyroxine-binding globulin; TSH, thyrotropin; tT_3 , 3,5,3'-triiodothyronine.

^aTwo-tailed, independent Student's t -test.

^bIodide urinary excretion in nmol iodine/mmol creatinine.

Table 4. Thyroid hormone and TSH concentrations compared between low and high exposure groups at the age of 11 weeks

	Low exposure		High exposure		p^a
	Mean \pm SEM	<i>N</i>	Mean \pm SEM	<i>N</i>	
tT_4 (nmol/l)	111.1 \pm 4.0	18	122.2 \pm 3.0	16	0.033
TBG (nmol/l)	519.0 \pm 29.4	18	500.7 \pm 13.0	16	0.57
tT_4 /TBG	0.220 \pm 0.008	18	0.247 \pm 0.009	16	0.040
TSH (mU/l)	1.81 \pm 0.19	18	2.50 \pm 0.26	12	0.044
tT_3 (nmol/l)	2.94 \pm 0.13	16	2.90 \pm 0.13	10	0.81
Iodide excretion ^b	971 \pm 99	17	1156 \pm 98	18	0.19

tT_4 , total 3,3',5,5'-tetraiodo-L-thyronine; TBG, thyroxine-binding globulin; TSH, thyrotropin; tT_3 , 3,5,3'-triiodothyronine.

^aTwo-tailed, independent Student's t -test.

^bIodide urinary excretion in nmol iodine/mmol creatinine.

and had to switch to bottle-feeding (powdered milk formula): 7 mothers after 5 weeks, two after 6 weeks, and 2 after 8 weeks (8 and 3 in the low and high exposure groups, respectively).

Breast-milk dioxin concentrations were between 8.7 and 28.0 ng TEQ/kg milk fat (mean 18.6) in the low exposure group and between 29.2 and 62.7 ng TEQ/kg milk fat (mean 37.5) in the high exposure group. This difference in dioxin concentration between both groups was highly significant ($p < 0.001$). Also, when only milk samples of mothers who breast fed for at least 11 weeks were considered, the difference in dioxin concentration was highly significant ($p < 0.001$). Concentrations of the 17 measured congeners in the milk fat are listed in Table 1 for both exposure groups. Birth weight and gestational age were similar in both groups (3.64 ± 0.09 versus 3.65 ± 0.12 kg and 40.2 ± 0.3 versus 40.4 ± 0.3 weeks in the low and high exposure groups, respectively). Six women had a history of cigarette smoking during pregnancy in the

Table 5. Change of thyroid hormone and TSH concentrations between birth and 1 week after birth compared between low and high exposure groups

	Low exposure		High exposure		p^a
	Mean \pm SEM	N	Mean \pm SEM	N	
tT_4 (nmol/l)	28.6 ± 5.6	18	45.7 ± 6.8	15	0.063
TBG (nmol/l)	5.1 ± 22.1	18	-29.6 ± 30.7	15	0.37
tT_4 /TBG	0.049 ± 0.012	18	0.095 ± 0.015	15	0.024
TSH (mU/l)	-7.5 ± 1.7	19	-9.2 ± 2.1	14	0.48

tT_4 , total 3,3',5,5'-tetraiodo-L-thyronine; TBG, thyroxine-binding globulin; TSH, thyrotropin.

^aTwo-tailed, independent Student's *t*-test.

low exposure group versus one in the high exposure group. Mean tT_4 and TBG concentrations and tT_4 /TBG ratios were similar in the mothers of both groups (data not shown).

The mean concentrations of hormones, TBG, and ratios determined in plasma of the infants at different times after birth are listed in Tables 2–4. The mean tT_4 concentrations at birth and 1 and 11 weeks after birth were higher in the high exposure group, but the difference was only significant 1 and 11 weeks after birth (see Fig. 1a,b). At these ages, the tT_4 /TBG ratio (as

indication for fT_4 concentrations) was also significantly higher in the high exposure group (see Fig. 1c,d). In addition, TSH concentrations were significantly higher at the age of 11 weeks in the high exposure group compared to the low exposure group (see Fig. 2). At birth and 1 week after birth, TSH concentrations were not significantly different in both groups. Mean concentrations of tT_3 , rT_3 , and fT_4 in cord plasma and tT_3 concentrations at the age of 11 weeks were not significantly different between both exposure groups. Urinary iodide excretion was similar in both exposure groups at the ages of 1 and 11 weeks. When only infants who were breast fed for at least 11 weeks were considered, no significant differences in tT_4 , TBG, and TSH concentrations could be found at the age of 11 weeks. However, the tT_4 /TBG ratio was still significantly higher in the high exposure group at this age [mean \pm SEM are 0.211 ± 0.011 and 0.246 ± 0.012 ($p = 0.047$) in the low and high exposure group, respectively].

The increase of tT_4 , TBG, TSH, and tT_4 /TBG ratio during the first week of life was compared between the high and low exposure groups. As shown in Table 5, both tT_4 ($p = 0.063$) and the tT_4 /TBG ratio ($p = 0.024$) increased more in the high exposure group.

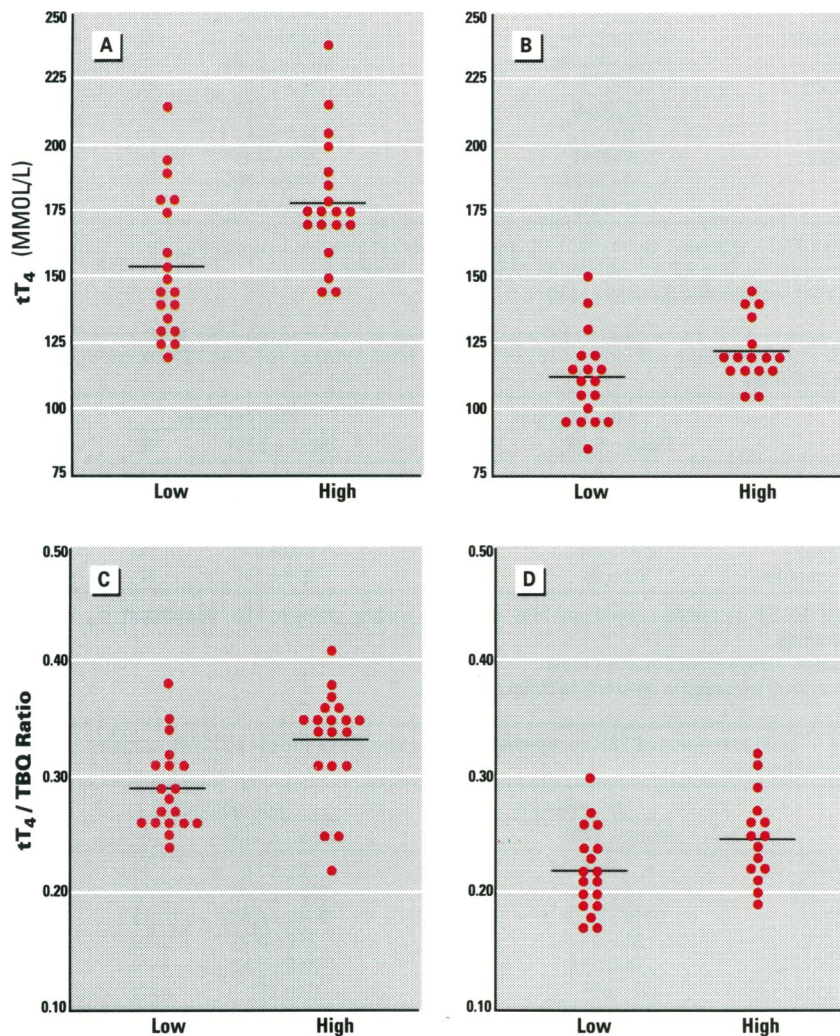


Figure 1. Distribution of total T_4 concentrations and tT_4 /TBG ratios of the subjects in the low and high exposure groups at the ages of 1 week (a,c) and 11 weeks (b,d). Each symbol represents one infant. Mean concentrations were significantly different.

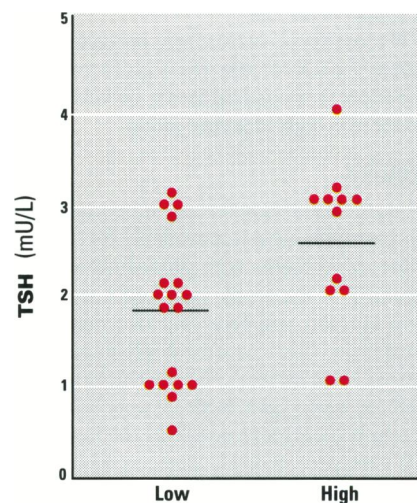


Figure 2. Distribution of TSH concentrations of the subjects in the low and high exposure groups at the age of 11 weeks. Each symbol represents one infant. Mean concentrations were significantly different.

Discussion

Comparing two groups of neonates, one with a relatively high exposure to dioxins as determined by breast-milk dioxin concentrations and one with a relatively low exposure, we observed that the mean tT_4 concentrations and tT_4 /TBG ratios were significantly higher at the ages of 1 and 11 weeks in the high exposure group. TSH concentrations were only significantly higher in the high exposure group at the age of 11 weeks. These significant differences between both exposure groups were preceded by a tendency for higher tT_4 concentrations in cord plasma in the high exposure group. Additionally, in the first week of life, tT_4 concentrations and the tT_4 /TBG ratio increased more in the high exposure group than in the low exposure group.

When only infants that were breast fed for at least 11 weeks were considered, mean tT_4 and TSH concentrations were still higher in the high exposure group at this age. However, the differences were no longer significant. This can, at least in part, be explained by the small number of infants breast fed for 11 weeks. The tT_4 /TBG ratios were still significantly higher in the high exposure group, indicating that free T_4 concentrations were higher in this group.

The higher tT_4 concentrations cannot be explained by differences in gestational age and birth weight because these were similar in both groups of infants. Neither can they be explained by the difference in smoking habits of the mothers. In a study of Meberg et al. (25), higher tT_4 concentrations in cord serum were found in the smoking group compared to the nonsmoking group. In our study, six of the seven smokers were in the low exposure group.

In animal studies, the effects of dioxins on the thyroid hormone concentrations depend on the species tested. Exposure to 2,3,7,8-TCDD was followed by elevated plasma tT_4 concentrations in the guinea pig (8) and by elevated tT_4 , tT_3 , and TSH concentrations in the hamster (9). In the rat, however, dioxin exposure caused a decrease of tT_4 concentrations (10,11–15), while tT_3 concentrations were unchanged (13–15,26) or increased (9,10,13), and TSH concentrations were elevated (10,12). Although dioxins change circulating hormone concentrations, rats were functionally euthyroid after administration of 2,3,7,8-TCDD (27–29).

Despite the different response of tT_4 concentrations between hamsters and rats, both species had increased TSH concentrations after exposure to 2,3,7,8-TCDD (10,12). Therefore, it is expected that in both species the thyroid gland is stimulated to increase T_4 synthesis. Reduced tT_4 con-

centrations in rats might be due to enhanced biliary excretion of T_4 by induction of uridine diphosphate-glucuronyltransferase (UDP-glucuronyltransferase) by the relatively high dose of TCDD administered. Induction of UDP-glucuronyltransferase, considered to be the rate-limiting enzyme for biliary T_4 excretion (30), has been observed for both dioxins (10) and PCBs (31). In hamsters, UDP-glucuronyltransferase is also induced, but absolute activities, expressed on the basis of whole livers, are about to fold lower than in rats (9). Therefore, the biliary excretion of T_4 in hamsters will be less induced, so that tT_4 concentrations can rise as a response of increased stimulation of the thyroid gland.

Regarding the results of the present study, we postulate that dioxins influence thyroid hormone concentrations in infants by interfering with the thyroid hormone regulatory system. First, the TBG concentrations are similar in both exposure groups, indicating that dioxins do not affect concentrations of the major thyroxine-binding protein. Second, there are significantly higher tT_4 concentrations and tT_4 /TBG ratios at the age of 1 and 11 weeks and higher TSH concentrations at the age of 11 weeks in the high exposure group. Because there is a structural similarity between the dioxin molecule and T_4 (32), dioxins might interfere with the transport of T_4 into the cell, the conversion of T_4 into T_3 , or the binding of T_3 to its nuclear receptor. In fact, an inhibition of the enzyme 5'-deiodinase, which results in decreased conversion of T_4 to T_3 , has been described by Rickenbacher et al. (33) for dioxin analogs. We hypothesize that dioxins might ultimately decrease the nuclear T_3 receptor occupancy. In the pituitary gland, a decreased nuclear T_3 receptor occupancy will stimulate TSH secretion. The resulting higher T_4 synthesis will subsequently result in an adequate receptor occupancy by T_3 , which compensates for the action of dioxins. In this way a new steady state develops with increased plasma concentrations of both tT_4 and TSH, resulting in functional euthyroidism in this clinically healthy group of infants.

The significantly higher tT_4 concentrations and tT_4 /TBG ratios in the high exposure group as compared to the low exposure group at the age of 1 week can hardly be explained by dioxin exposure via breast milk alone because the intake of milk during the first week of life is relatively low. Additionally, there was already a trend toward higher tT_4 concentrations in cord plasma. Considering the finding that dioxins are present in fetal adipose tissue and liver (7,34–37), we presume that the higher tT_4 concentrations result from intrauterine exposure to these compounds,

although the role of exposure after birth cannot be excluded. Dioxins are accumulated in adipose tissue because of their lipophilicity. In the first days of life, fatty acids are mobilized from the brown adipose tissue to maintain body temperature (38). This may cause an increased release of dioxins, resulting in circulating dioxin concentrations high enough to affect the target organs.

This importance of prenatal exposure is in accordance with the results of some epidemiologic studies in which prenatal exposure to PCBs was related to disorders in neurological development. Rogan et al. (39) found a relation between transplacental exposure to PCBs and hypotonicity and hyporeflexia in the first week of life. A relation between *in utero* exposure to PCBs and poorer short-term memory function at the age of 4 years has been reported by Jacobson et al. (40). In both studies, no relation was found with postnatal exposure by breast milk. This indicates that transplacental exposure to PCBs, although smaller than exposure via breast milk, is more important. Whether the neurological disorders found by Rogan and Jacobson are related to dioxin- or PCB-induced changes in thyroid hormone concentrations remains unclear.

The higher tT_4 concentrations and tT_4 /TBG ratios in the high exposure group at the age of 11 weeks might be due to prolonged effects of intrauterine exposure to dioxins because of the long half-lives of dioxins in humans (5–8 years) (41,42). The fact that TSH concentrations were significantly higher in this group suggests that at 11 weeks the influence of dioxins on the hypothalamic–pituitary–thyroid axis has become even more pronounced. At this age it is likely that, in addition to the postulated long-term effects of intrauterine exposure to dioxins, exposure to these compounds via breast milk may play a role. However, the change in circulating tT_4 and TSH concentrations does not prove that functional thyroid status has been affected by pre- and postnatal exposure to dioxins.

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