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T. Bajanowski · P. Fürst · K. Wilmers · J. Beike
H. Köhler · B. Brinkmann

Dioxin in infants – an environmental hazard?

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Abstract The concentrations of the most common dioxin and dibenzofuran congeners were measured in different tissues (e.g. liver, kidneys, subcutaneous fatty tissue and spleen) from 27 infants who died suddenly and unexpectedly. The cases could be subdivided into 2 groups consisting of 15 infants who died in 1991/1992 and in 12 infants who died in 1996/1997. The autopsies were carried out using a standardised protocol and additionally the parents were asked to supply details of the nutritional conditions. The age of the mother and the birth order of the infants were also recorded. From the results obtained by correlating these parameters with the dioxin concentrations three main factors could be established: 1) there was a significant decrease in the total dioxin concentration in infant tissues from 1991/1992 to 1996/1997 indicating a decrease in the environmental dioxin levels due to a decrease in dioxin emission, 2) the birth order was inversely and the duration of breast feeding directly proportional to the dioxin concentrations thus showing that the mothers can decontaminate themselves by breast feeding and 3) an accumulation of specific dioxin congeners was observed in the liver tissue but the pathophysiological significance of these observations is not yet fully understood. Because of the well-known beneficial effects of breast feeding and considering the results of the present study, this type of infant nutrition can be recommended without any restrictions.

Keywords Infant death · Dioxin uptake · Breast feeding · Tissue concentration

T. Bajanowski (✉) · J. Beike · H. Köhler · B. Brinkmann
University of Münster, Institute of Legal Medicine,
Röntgenstrasse 23, 48149 Münster, Germany
e-mail: bajano@uni-muenster.de, Fax: +49-251-8355158,

P. Fürst · K. Wilmers
Chemical and Veterinary State Control Laboratory,
Sperlichstrasse 19, 48151 Münster, Germany

Introduction

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are formed from organic substances and organic or inorganic chlorine. These substances are released into the environment from industrial fumes, combustion residues and as by-products from the chlorine industry, and are found ubiquitously [1].

The level of bio-accumulation leads to a considerable body burden in the population. Due to the lipophilic properties of PCDDs and PCDFs these substances were found to be especially enriched in fatty tissue [2, 3]. In humans the main source is from nutrition. Human milk is especially high in these harmful substances [3, 4] and a typical distribution pattern of congeners was found in milk. The daily dioxin intake of breast-fed infants calculated from concentrations in human milk can be up to 50-fold higher than in adults [5] which led to the suspicion that this could influence the infants' health. PCDDs and PCDFs are normally not found as single compounds but as complex mixtures. In order to facilitate the comparison of analytical data, it has proven useful to convert the analytical results into toxic equivalents (TEQ). This conversion is based on the assumption that all PCDD/PCDF congeners show comparable qualitative effects, binding to the same AH-receptor (aryl hydrcarbon), but with different intensities. The different binding activity is expressed by toxic equivalency factors (TEF) estimated from the weaker toxicity of the respective congener in relation to the most toxic compound 2,3,7,8-tetrachloro-dibenzo-p-dioxin, which is assigned the arbitrary TEF of 1. Moreover, it is assumed that the effects are nor synergistic or antagonistic, but additive. By multiplying the amount of each congener analytically determined with the corresponding TEF, the final result is the TEQ value of a sample. The daily intake of adults living in industrialised countries varies between 1–3 pg TEQ/kg body weight [6].

The aim of the present study was to determine PCDD and PCDF levels in tissues of deceased infants and to examine the influence of different types of feeding and other parameters on the body burden of these chemicals.

Table 1 The main epidemiological data of the mothers and infants, and the dioxin concentrations (I-TEq, ng/kg fat) in fatty tissue and the liver are given as summary statistics (arithmetic mean; the standard deviation is added only for important parameters). The relative amount of breast feeding was calculated as time of exclusively breast feeding (weeks) +0.5× time of partially breast feeding (weeks)/age in weeks at death × 100 (*BMI* body mass index)

Cases		N	Average age mothers (Years)	Birth order of infants	Average age infants (Weeks)	Average BMI	Breast feeding (%) Relative amount	Average I-TEq levels (ng/kg fat)	
Year	Number							Fatty tissue	Liver
1991/1992	1– 5	5	26.8	1, 2, 2, 3,3	24.6	17.72	0	5.1 ± 5.3	9.6 ± 3.5
	6– 9	4	25.2	2, 2, 2, 2	25.5	17.94	21.2	13.1 ± 9.9	34.6 ± 21.9
	10–15	6	32.8	1, 2, 3, 3, 3, 4	21.5	15.61	91.3	42.6 ± 20.8	137.1 ± 74.2
1991/1992	Total	15	28.8 ± 5.8		23.6 ± 13.3	16.93	42	22.2 ± 22.2	56.5 ± 69.6
1996/1997	16, 17	2	32.5	2, 5	22.0	15.33	0	1.2	2.2
	18–24	7	27.4	1, 1, 1, 2, 3, 4, 4	24.7	16.46	23.6	4.0 ± 4.6	6.6 ± 7.6
	25–27	3	30.0	2, 3, 4	9.0	15.66	100	13.2 ± 7.5	14.0 ± 8.1
1996/1997	Total	12	28.9 ± 4.9		20.3 ± 12.3	16.07	39	5.9 ± 6.7	7.7 ± 8.1

Material and methods

In 15 randomly selected infants who died suddenly and unexpectedly during the years 1991 and 1992 (from the Westfalian cot death study) and in 12 infants who died in the same area in 1996 and 1997 (all cases from October 1996 to February 1997, pilot phase of the German National cot death study), an autopsy was performed using a standardised autopsy protocol similar to the international standardised autopsy protocol [7] including extensive histology, toxicology, microbiology, virology and clinical chemistry. An adequate cause of death could not be found in these cases and the final diagnosis was sudden infant death. Subsequently the parents were interviewed and asked for the mother's age at birth, the birth order of the victim, the duration of breast feeding (full and partial) and for the type of additional food given (Table 1).

The tissues obtained during autopsy were stored in sterile glass tubes at a temperature of –20 °C up to the investigation. The specimens were ground with sodium sulphate and sea sand followed by column extraction using hexane/acetone. Subsequent analytical steps comprised spiking with ^{13}C-labelled PCDD/PCDF, clean-up using sulphuric acid-coated silica gel, florisil and carbon columns, separation by capillary gas chromatography and determination by high resolution mass spectrometry (HRMS) at a resolution of $R = 10{,}000$ in the selected ion recording mode (SIR). The long-term stability of the method has been tested and proven by analysing three different quality control pools over a period of several years. The concentrations of the most common 17 dioxin and dibenzofuran congeners were determined in the liver, the kidneys, the spleen and in fatty tissue by high resolution gas chromatography-high resolution mass spectrometry (HRGC-HRMS). All the analytical methods used have been previously described in detail [3, 8, 9, 10, 11].

Statistical analysis to characterise differences in dioxin concentrations between the different groups and time periods was carried out using the *t*-test.

Results

The total dioxin concentrations decreased between 1991/1992 and 1996/1997 to 10–30% in the liver and the fatty tissue independent of the duration of breast feeding (Table1). For some dioxin congeners (e.g. OCDD, 1,2,3,4,6,7,8-HpCCD, OCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF and 2,3,4,6,7,8-HxCDF) a notable accumulation in the liver fat could be observed (Tables 2 and 3) while the concentrations of other congeners did not differ significantly from organ to organ. As typical for human samples the congeners 1,2,3,7,8-PeCDF, 1,2,3,7,8,9-HxCDF and 1,2,3,4,7,8,9-HpCDF were only found in some cases and the concentrations were near the detection limit (concentrations are not given in Tables 2 and 3).

In both time periods infants with a long period of breast feeding showed higher total dioxin concentrations than infants with a shorter period of, or no breast feeding (Table 1, Fig. 1). If the average I-TEq levels in the fatty tissue are compared, the dioxin concentrations in predominantly breast-fed infants (relative amount of breast feeding > 80%) were 7-fold (1991/1992) to 10-fold (1996/1997) higher than in exclusively formula-fed infants (Table 1). This cannot be an age-related phenomenon because the age distribution in the two groups is similar (especially in 1991/1992, Table 1). Only the relatively low average age of the exclusively breast-fed infants in 1996/1997 could have in-

Table 2 The concentrations of 14 different PCDD/PCDF congeners are given for totally and partially breast-fed infants in the liver and adipose tissue (mean, median, range) and the ratios (liver concentration/ concentration in adipose tissue) based on fat weight are calculated

PCDD/PCDF concentration in adipose tissue and liver of exclusively and partially breast fed infants (ng/kg fat, $N = 20$)							Ratio Liver:fat
Congener	Adipose tissue			Liver			
	Mean	Median	Range	Mean	Median	Range	
OCDD	109.4	48.1	12.0–316.0	1224.9	586.0	33.8–6550.0	11.2
1,2,3,4,6,7,8-HpCDD	24.0	9.3	1.4– 79.0	200.1	56.4	4.4– 997.0	7.0
1,2,3,4,7,8-HxCDD	5.5	2.7	0.2– 24.2	11.6	4.0	0.2– 61.0	1.7
1,2,3,6,7,8-HxCDD	24.7	10.3	0.6–112.0	30.5	10.3	0.5– 144.0	1.1
1,2,3,7,8,9-HxCDD	3.2	2.4	0.2– 11.2	5.9	2.0	0.2– 32.0	1.5
1,2,3,7,8-PeCDD	6.2	2.8	0.2– 29.2	7.2	2.8	0.2– 31.5	1.1
2,3,7,8-TeCDD	2.5	1.2	0.1– 12.9	2.2	1.0	0.1– 12.0	0.8
OCDF	0.4	0.4	0.1– 0.8	6.5	4.6	0.6– 19.0	16.9
1,2,3,4,6,7,8-HpCDF	2.8	1.7	0.3– 11.7	27.9	14.2	1.1– 140.0	9.3
1,2,3,4,7,8-HxCDF	4.9	2.9	0.5– 24.7	41.1	12.6	1.2– 203.0	7.8
1,2,3,6,7,8-HxCDF	3.4	2.0	0.2– 17.5	37.0	10.5	0.8– 193.0	9.9
2,3,4,6,7,8-HxCDF	1.2	0.7	0.1– 6.0	11.0	2.9	0.2– 51.9	7.5
2,3,4,7,8-PeCDF	12.9	4.8	0.5– 78.2	39.6	15.1	0.8– 218.0	2.7
2,3,7,8-TeCDF	0.7	0.6	0.2– 1.7	1.0	0.7	0.3– 3.0	1.4
I-TEq	16.8	8.0	0.7– 87.4	43.0	17.9	1.7– 215.8	2.3

Table 3 The concentrations of 14 different PCDD/PCDF congeners are given for non-breast-fed infants in the liver and adipose tissue (mean, median, range) and the ratios (liver concentration:concentration in adipose tissue) based on fat weight are calculated

PCDD/PCDF concentration in adipose tissue and liver of non-breast-fed infants (ng/kg fat, $N = 7$)							Ratio Liver:fat
Congener	Adipose tissue			Liver			
	Mean	Median	Range	Mean	Median	Range	
OCDD	28.54	19.5	12.0–75.0	398.2	325.0	174.0–800.0	19.1
1,2,3,4,6,7,8-HpCDD	4.4	2.8	1.3–11.8	36.7	27.0	14.3– 74.0	10.4
1,2,3,4,7,8-HxCDD	1.4	0.9	0.1– 4.5	1.7	1.4	0.3– 3.8	1.7
1,2,3,6,7,8-HxCDD	5.5	3.3	0.9–20.1	4.4	3.6	0.5– 12.0	0.9
1,2,3,7,8,9-HxCDD	0.8	0.5	0.1– 2.9	0.7	0.6	0.1– 1.7	1.2
1,2,3,7,8-PeCDD	1.5	0.9	0.2– 5.4	1.3	1.0	0.3– 4.0	1.0
2,3,7,8-TeCDD	0.6	0.4	0.1– 2.1	0.6	0.4	0.1– 1.5	1.2
OCDF	0.5	0.5	0.2– 0.6	7.2	5.4	1.5– 20.0	17.7
1,2,3,4,6,7,8-HpCDF	1.4	0.4	0.3– 5.5	13.2	7.4	5.2– 34.0	14.7
1,2,3,4,7,8-HxCDF	1.5	0.8	0.2– 4.8	7.8	7.8	2.3– 13.0	10.3
1,2,3,6,7,8-HxCDF	0.9	0.5	0.2– 3.1	7.6	7.6	2.0– 12.0	12.7
2,3,4,6,7,8-HxCDF	0.2	0.2	0.1– 0.4	1.7	1.6	0.5– 3.3	8.7
2,3,4,7,8-PeCDF	3.8	2.2	0.5–13.8	7.5	7.1	1.1– 15.2	2.7
2,3,7,8-TeCDF	0.4	0.3	0.2– 0.5	0.8	0.6	0.4– 2.3	2.4
I-TEq	4.4	2.5	0.6–15.6	8.3	7.6	1.8– 15.6	2.8

fluenced the low dioxin concentration in this group due to a lower total dioxin intake. The total decrease in tissue concentrations from 1991/1992 to 1996/1997 varied between 69% for predominantly or exclusively breast-fed infants and 76% for formula-fed infants and shows no significant differences comparing the groups. The increase of total dioxin concentration in the tissue is highest during the first 10 weeks of life and seems to remain constant after this time (Fig. 2). Higher dioxin levels were detected in victims who did not have older breast-fed siblings. Among infants with the same birth range those who were not breast-fed showed the lowest dioxin concentrations.

Based on the average dioxin concentrations determined in the fatty tissue (dioxin concentration at death/age at death in weeks) the dioxin uptake can be calculated for the different groups (Table 4) and it is obvious that the weekly dioxin uptake is about 10- to 25-fold higher in breast-fed than in formula-fed infants.

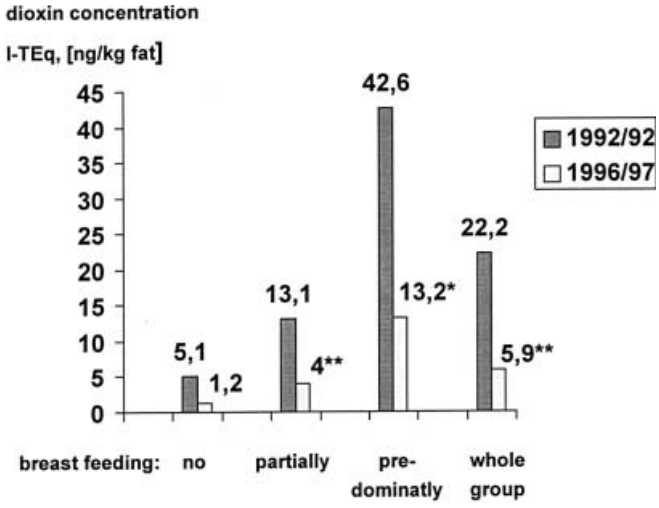

Fig. 1 Average dioxin concentrations in fatty tissue in the two time periods. The groups are defined depending on the type of nutrition. The comparison of dioxin concentrations in the different time periods (1991/1992, 1996/1997) shows significant differences for the groups investigated (*$p < 0.1$, **$p < 0.05$)

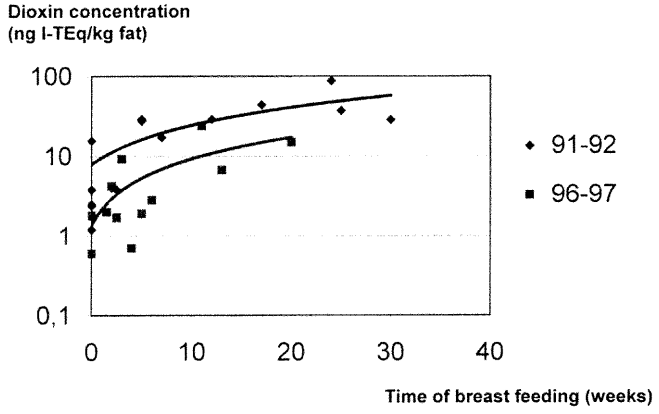

Fig. 2 Dioxin concentrations in fatty tissue (I-TEq, logarithmic scale) dependent on the duration of breast feeding. The trend lines (generated by PC using Microsoft Excel for linear regression) for the two time intervals run in parallel

Table 4 Calculated average dioxin intake per week (dioxin concentration at death/age at death in weeks) in the different time periods (1991/1992 and 1996/1997) in infants which were not or predominately breast-fed

Time period	Average weekly dioxin intake (I-TEq levels, ng/kg fat)	
	No breast feeding	Predominantly breast-fed
1991/1992	0.21	1.98
1996/1997	0.06	1.47

Discussion

It is known that breast feeding plays a special role in dioxin uptake because the dioxin concentrations in human milk are much higher than in other food [3, 4, 5]. Dioxins stored in the maternal fatty tissues are mobilised during periods of breast feeding and accumulate in the fat-rich human milk [3, 4, 5].

Since the Seveso incident, one main symptom caused by acute dioxin exposure is particularly well-known, so-called chloracne. Furthermore small changes of liver function (activity of γ-GT and aminotransferase) and an increased excretion of glucaracide in urine have been reported [12]. Subsequently toxic effects of dioxins were suspected and investigations were carried out using animal models. A single gestational dose of TCDDs in rats had reproductive effects on the pups and young male rats leading to a reduced number of spermatozoa [13]. In female rats the same treatment caused a higher number of genital malformations [14]. Other authors [15, 16] reported that dioxin has effects on the developing immune system with an imbalance of lymphocyte populations. In monkeys a higher rate of endometriosis [17] and neurological disturbances [18] could be observed after dioxin exposure. Investigations of dioxin effects in humans, especially in infants and children are rare. Neurodevelopmental effects [19], changes in lymphocyte populations [20] and changes in the concentrations of thyroid hormones [2, 21, 22] were reported and a modulation of the function of the hypothalamic-pituitary-thyroid system in newborns that was induced by dioxin exposure was assumed [22]. However the significance of all these observations is still unclear. Recently, Mocarelli et al. [23] reported a relative increase in the number of female births after the fathers had been exposed to high levels of dioxins when they were younger than 19 years of age.

In 1990 Beck et al. [24] determined PCDD/PCDF concentrations in tissue samples obtained from three SIDS victims and found surprisingly low levels of between 2.1 and 3.4 ng of I-TEq/kg of fat in the adipose tissue. In 1994 the same authors reported dioxin concentrations in five further SIDS cases ranging between 2.1 and 36 ng I-TEq/kg fat (average 11 ng/kg) [5]. However, only the two infants with the longest breast feeding periods showed I-TEq levels higher than 10 ng/kg fat while the tissue concentrations of the other partially breast-fed infants and infants who had received only formula food did not differ significantly. Possible explanations for the different I-TEq levels reported by Beck et al. [5, 24] and those in the present study, which are in accordance with Abraham et al. [25], could be a higher birth range in the infants investigated by Beck et al. thus leading to lower tissue concentrations or statistical coincidence due to the low number of cases investigated. Regional differences of the PCDD/PCDF concentrations in human milk in Germany as a further theoretical cause seem to be very unlikely and were not reported in the literature [26].

The decrease of dioxin concentrations in the tissues of breast-fed infants from 1991/1992 to 1996/1997 is the result of lower PCDD/PCDF concentrations in the human milk which decreased during this time period to about 50% (Fig. 3) In non-breast-fed infants the decrease must be due to a clear reduction in dioxin levels in formula foods indicating generally lower emission rates of dioxin and a less polluted environment in Germany [27].

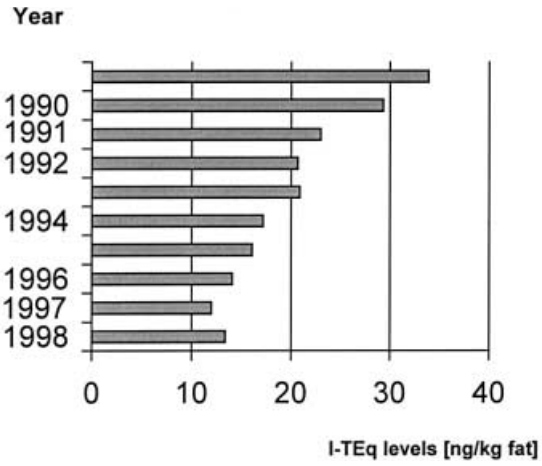

Fig. 3 Changes in PCDD/F concentrations in human milk in Germany from 1989 to 1998 (unpublished data of the Chemical and Veterinary State Control Laboratory of Northrhine Westfalia, Germany). A total of 741 samples (between 19 and 281 per year) were investigated

The PCDD/PCDF body burden of mothers decreases during the lactation period to about 90 to 70% of the previous level [5, 28]. The mothers are able to "decontaminate" themselves by breast feeding [5, 25, 27, 28] so infants with a low birth order and long periods of breast feeding show higher dioxin concentrations in the tissues than infants with high birth orders, short periods of breast feeding or non-breast-fed infants. An alternative or additional explanation is that the higher birth order infants could benefit because the mother's body burden decreased with time due to lower levels of environmental exposure.

Furthermore it is obvious that the highest daily intake is reached during the first weeks of breast feeding (Fig. 2), while the intake decreases during an on-going breast feeding period. Abraham et al. [25] found a decrease in the exposure per kg of body weight in 5-month-old breast-fed infants and described this phenomenon to be caused by growing and additional food. The results of the present study show that there is also a lower increase of dioxin concentrations in the tissue after the 10th week of life. It can be assumed that this phenomenon may be dependent on decreasing dioxin concentrations in the mothers fatty tissue caused by on-going decontamination by breast feeding as well as by an increasing amount of additional formula food after the 10th week or by a non-proportional increase of body weight and daily intake of food.

It is not possible to give an explanation for the particular accumulation of some dioxin congeners in the liver. It can only be speculated that the affinity of different congeners to biochemical receptors or substances differs and that these congeners could have a different affinity to the aryl hydrocarbon (AH) (dioxin) receptor. This receptor influences the transcription of a battery of genes encoding drug-metabolising enzymes, e.g. cytochrome P450 1A1, 1A2, 1B1, glutathione-S-transferase and UDP-glucuronosyl-transferase [29]. Furthermore the receptor is thought to be responsible for immediate activation of tyrosine kinases [12]. One of the main toxicokinetic determinants of dioxins could be the binding to cytochrome P450 1A2 in the liver leading to hepatic sequestration of TCDD [29]. This mechanism in particular could be responsible for the known changes in liver functions.

One of the main difficulties in investigations dealing with environmental toxicology in humans, is that a wide variety of biologically active substances are found ubiquitously and therefore it is very difficult to differentiate between effects of single environmental substances or groups of substances. Other substances with biological effects of interest are, for example polychlorinated biphenyls (PCBs) [30, 31] or methylmercury [32, 33]. In particular, the question of possible synergistic effects of these environmental substances on human development is unclear.

According to the results of some epidemiological studies, among others the Westfalian cot death study where breast feeding could be characterised to be a protective factor for SID [34, 35, 36, 37, 38], it can be assumed that dioxins in human milk do not seem to significantly influence the risk for SID. At present this conclusion can be drawn only indirectly because the "normal range" of dioxin levels in tissue samples of infants of different age is not sufficiently defined.

With regards to the well-known advantages of breast feeding, and considering the results of the present study showing a significant decrease in dioxin concentrations not only in human milk but also in infant tissue samples, it seems reasonable to recommend unrestricted breast feeding especially in industrialised countries with an effective environmental protection policy.

The new WHO recommendations [6, 29] could be a further contribution to reduce the daily intake and as a prerequisite the dioxin emission. The tolerable daily intake (TDI) is defined as 1–4 pg TEQ/kg body weight over the whole life-span and includes in addition to the dioxin congeners 15 dioxin-like PCBs. For reasons of prophylactic health protection the aim should be to accept the lower limit as the gold standard. This would be a challenge even to western industrial nations and necessitate further reduction of dioxin emission and consequent control of environmental input sources.

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