Breastmilk, PCBs, dioxins and vitamin K deficiency: discussion paper

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In this paper the hypothesis is discussed that polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxines (PCDDs) and polychlorinated dibenzofurans (PCDFs) present in breastmilk in industrial countries cause the late haemorrhagic disease of the newborn.

Late haemorrhagic disease in the newborn (HDN) is a rather new disease entity described as such in 1985 by Lane1. He starts his description with the following sentence ‘During the past ten years it has become apparent that vitamin K deficiency hemorrhage is an important cause of morbidity and mortality in infants older than 1 month’. He differentiates the disease into three periods: (1) The early form: 0–24 h after birth; (2) the classic form: 1–7 days after birth; (3) the late form: 1–3 months after birth. The classic form and the early form are described by van Creveld in 1957 and he emphasizes the life threatening coagulation problems in the perinatal period caused by anti­convulsants, especially phenobarbital and dilantin, used by the mother. He did not describe the possibility of a late form of haemorrhagic disease in exclusively breastfed infants. In those years in Holland 70% of the babies were delivered at home and exclusively breastfed. No vitamin K was given after birth; this was never routine in Holland.

The large series of 425 infants with the late form of the haemorrhagic disease of the newborn reported from Japan was seen during a three year period (1978–1980). Of these 425 infants, in 91 cases the vitamin K deficiency could have been secondary to specific disorders such as congenital bile duct atresia, chronic diarrhoea or alpha-1 antitrypsine deficiency. In 334 infants vitamin K deficiency was idiopathic, of which 286 were exclusively breastfed and 48 partially. Intracranial haemorrhage was present in 87%. In the late form more intracranial haemorrhage was seen contrary to the classic form which has more gastrointestinal bleeding, well-known as melaena neonatorum.

McNinch reported six cases from 7000 deliveries during a 17-month period in Devon (1:1200) in 19844. He speaks of a resurgence of HDN and blames other infant feeding policy such as the increase in breastfeeding and the advice to mothers to avoid cow’s milk formula. Sutor reported similar cases5.

Vitamin K deficiency in the newborn secondary to the use of medicaments is described for anti­convulsants, n-methylthiotetrazole-cefalosporins, rif­ampicin, isoniazid, salycylates, ethyl morfins, alcohol and coumarin. Because of cases of severe late HDN in Holland, Widdershoven studied prospectively the idiopathic or primary late HDN in a group of breastfed babies versus a group of bottlefed infants in 1985–19866. No vitamin K was given after birth.

In cordblood in 6–10% PIVKA (Prothrombin in vitamin K absence) infants were detected. At 30, 60 and 90 days after birth, ±10% of infants demonstrated PIVKA in the breastfed group, with different infants detected at each test. No PIVKAs were detected in the bottlefed group in the first months of life. None of the breastfed infants had clinical signs of a bleeding diathesis, the PIVKA levels were much lower than usual in severe coagulation disorders. However, ten years earlier Van Doorm was not able to show any PIVKA in 43 cordblood samples in Holland7.

Motoharas reports 10 cases of severe idiopathic vitamin K deficiency in breastfed infants aged 27–47 days.8 The hypothesis that a low vitamin K level in breastmilk was the cause could not be confirmed. The vitamin K level was low in only three breastmilk samples, in the seven others it was normal and even high in milk for a baby with a severe intracranial haemorrhage.

Other attempts to blame a dietary deficiency due to an inadequate intake of vitamin K by the mothers, have proved inconclusive9.

Late HDN is also seen in England after the administration of vitamin K after birth10.

In conclusion, late haemorrhagic disease of the newborn is probably a new disease entity, seen in the 1980s in exclusively breastfed babies and is characterized by intracranial haemorrhage.

Breastmilk in industrialized countries is contaminated with polychlorobiphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). In 1966 Jensen in Sweden reported a new chemical hazard in breastmilk, the well-known PCBs11. Dioxins and furans in breastmilk were first reported by Rappe in 1984 in milk of mothers living in north Sweden and western Germany, areas not thought of as contaminated with dioxins12. Because of the striking similarities in toxicity and environmental fate, and the fact that all three (PCBs, PCDDs and PCDFs) are present in breastmilk in industrialized countries the three chemicals are usually discussed together.

PCBs were produced in large quantities in chemical factories because of their properties of insulation and non-inflammability and they were used in transformers and capacitors (closed systems) and in carbonless copypaper and wood preservative (open systems).

In Holland, PCBs were never manufactured but the pollution of the Dutch environment with PCBs is among the highest in the world due to the level of chemicals present in the rivers Rhine and Meuse. In Leiden, breastmilk of 23 mothers was analysed for PCBs13. A mean of 1.48 mg/kg fat PCBs was detected at each test. No PIVKAs were detected in the breastfed group, with different infants detected.
measured. This amount is similar to measurements in Denmark\textsuperscript{24} and western Germany\textsuperscript{25}.

**Dioxins and furans**

PCDDs and PCDFs are the inevitable byproducts of industrial chemical products such as the herbicide 2,4,5T, wood preservatives (pentachlorophenol) and bactericides (hexachlorophene). The most toxic dioxin is 2,3,7,8\textsubscript{TCDD}. The toxicity of other dioxins and furans is expressed as TCDD equivalents. For instance, 2,3,4,7,8 pentachlorodibenzofuran has a toxicity of 0.5 compared to TCDD. Olie reported the occurrence of PCDDs and PCDFs in fly ash and flue gas of municipal incinerators in the Netherlands in 1977\textsuperscript{16}.

Fuerst published results of 200 samples of breastmilk, collected in North-Rhine Westphalia, an area close to Holland\textsuperscript{17}. His results show that 2,3,4,7,8 \textsubscript{PCDD} is the main toxic compound in breastmilk. Octachlor dibenzodioxin (OCDD) represents more than 50\% of the total dioxins and the levels of the other isomers decrease with decreasing grade of chlorination. All isomers were identified as 2,3,7,8 chlorine substituted.

In 1985, milk of 12 Dutch mothers collected in our neonatal department was studied by Martin van den Berg\textsuperscript{18}. His results are in accordance with Rappe and Fuerst. Interestingly, no xenobiotics were detected in milk of a woman who had just immigrated to Holland from Surinam, although they were detected in a Surinam woman who immigrated 15 years ago to Holland.

It is known that PCBs, PCDDs and PCDFs are a mixture of isomers. They can induce enzymes in the liver such as phenobarbital or 3-methyl-cholanthrene. The Scientific Review Committee of the American Academy of Clinical Toxicology\textsuperscript{19} describes the clinical signs in adults chronically poisoned with dioxins. These are chloracne, hyperpigmentation, hirsutism, liver cirrhosis, polynepropathies and tiredness. Laboratory signs include increase in liver enzymes, prolonged prothrombin time, and an increase in cholesterol and triglycerides. The review ends with the remark that physicians should be instructed to look for the possible manifestations of TCDD exposure: chloracne, soft tissue masses, muscle pain, fatigue, peripheral neuropathy, tender hepatic enlargement, elevated liver enzymes, elevated lipids, prolonged prothrombin time, haemorrhagic cystitis and hirsutism.

The clinical signs in newborns from mothers intoxicated with rice oil containing PCBs, PCDDs and PCDFs were: growth retardation and smaller head circumference, dysplastic nails (coloured brown), hirsutism, a history of natal teeth and tooth chipping\textsuperscript{20}. Hara published data on children nursed with PCB contaminated milk\textsuperscript{21}. He found fatigue, fever, anorexia, abdominal pain, vomiting, red eyes with a discharge, wheezing, cough, eczema and itchy skin. He did not mention a prolonged prothrombin time. Monkeys exhibited fatty liver, pancreatic atrophy and fibrosis, bile duct proliferation and haemorrhage in the gastrointestinal tract after a high dose\textsuperscript{22}.

In the millions of chickens that have died due to polluted food subepicardial haemorrhage is seen\textsuperscript{23}. TCDD has been shown to produce cleft palate in several strains of mice, subcutaneous oedema, haemorrhage and dilated renal pelvices in rat and mice\textsuperscript{24}.

In the Seveso incident the most notable effect was chloracne. Six years later, the children exposed to the highest concentration of TCDD showed alterations in serum \gamma-glutamyltransferase and alanineaminotransferase activity compared with a control group. The observed abnormalities were slight and disappeared with time\textsuperscript{25}. Prenatal exposure to polychlorinated biphenyls, measured by cordserum PCB-levels was associated with lower birthweight and smaller head circumference. The mothers had eaten PCB-containing fish from Lake Michigan. Non-fish-eaters used as the controls\textsuperscript{26}. Jacobson showed that intrauterine PCB exposure has a delayed effect on central nervous system functioning in a dose dependent fashion\textsuperscript{27}.

Biochemically it is not known how the enzyme-inducer phenobarbital interferes with vitamin K metabolism in the perinatal period, but it is a clinical fact\textsuperscript{1}. In general, the vitamin K-levels are low in the cordplasma\textsuperscript{28}. From studies in rats, Poland found that dioxins induce DT-diaphorase\textsuperscript{29}. This enzyme is important to protect the rat hepatocyte against \textit{O\textsubscript{2}}-toxicity by menadione and helps to excrete menadiones\textsuperscript{30}. It is not known if extrapolation to the human situation is appropriate. If it is, then the induced enzyme may increase vitamin K metabolism by enhancing its excretion in bile. However, research on enzyme DT-diaphorase has shown the specific activity to be highest in tissues of the gastrointestinal

<table>
<thead>
<tr>
<th>Sample</th>
<th>TCDD (ng/kg milkfat)</th>
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<tbody>
<tr>
<td>EP 6</td>
<td>13.84</td>
</tr>
<tr>
<td>EP 17</td>
<td>16.82</td>
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<tr>
<td>EP 11</td>
<td>10.47</td>
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<td>EP 3</td>
<td>6.96</td>
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<td>EP 2</td>
<td>5.35</td>
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<td>EP 4</td>
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<td>EP 15</td>
<td>7.58</td>
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<tr>
<td>EP 12</td>
<td>6.25</td>
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<tr>
<td>BR 1</td>
<td>6.21</td>
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<tr>
<td>A 4</td>
<td>6.13</td>
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<tr>
<td>RW 1</td>
<td>7.20</td>
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</tbody>
</table>

| Mean   | 9                   |

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**Table 1. Mean dioxin and furan content in breastmilk of 14 mothers (17 samples)**

<table>
<thead>
<tr>
<th>Sample</th>
<th>TCDD (ng/l)</th>
<th>Milk fat (ng/kg)</th>
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<tr>
<td>EP 1</td>
<td>9.07</td>
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<tr>
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<td>6.13</td>
<td>5.35</td>
</tr>
<tr>
<td>RW 1</td>
<td>7.20</td>
<td>9.07</td>
</tr>
</tbody>
</table>

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**Table 2. TCDD content in 14 samples of breastmilk from 14 mothers**

**Bleeding:**

- Early: intracranial haemorrhage
- Intravent. haemorrhage
- Late: intracranial haemorrhage
- Foot bleeding

**No bleeding**

- EP 1
- EP 9
- EP 3
- EP 2
- EP 4
- EP 15
- EP 12
- BR 1
- A 4
- RW 1

**Mean**

9
tract and abdominal fat. In contrast to rodent liver, the human liver has extremely low DT-diaphorase activity. Tissue activity was found to be highly variable among the patients studied which suggests that nutritional and/or genetic factors may be involved, and the authors question the importance of DT-diaphorase in the human liver.

In 1987, 17 samples of breastmilk were collected from 14 mothers in our neonatal department. The results of the mean dioxin and furan content are given in Table 1. In Table 2 the TCDD content is given in 14 samples of 14 mothers. The infant fed breastmilk EP11 had severe intracranial haemorrhage on day 22 after birth. He was a fullterm baby who received no vitamin K after birth and was exclusively breastfed. He had a typical primary late HDN. In one case, EP 16, an infant born prematurely, had bleeding from his feet due to vitamin K deficiency three weeks after birth. In the first week of life he was loaded with vitamin K intramuscularly and intravenously. After the first week he was exclusively breastfed, but also received amoxycillin orally, perhaps interfering with absorption. A first-born infant fed breastmilk EP 6, had an intracranial haemorrhage on the second day of life. No clotting tests were done but vitamin K i.m. was then given. Because of these problems breastfeeding was stopped immediately after birth. Dioxins were determined in breastmilk of this mother breastfeeding her second baby born a year later, who received vitamin K immediately after birth. EP 17 is breastmilk of a 34 year old mother with a 28 week baby having an intraventricular haemorrhage on the second day of life. He received vitamin K 0.5 mg i.m. immediately after birth. In breastmilk of the other 10 mothers one high dose was detected (EP 9). This was in the milk of a primipara, 38 years old, with an extremely dysmature infant (880 g, 28 weeks gestation).

Even in this small number of samples it is clear that there is variation between individual mothers, as was found previously by Van den Berg in the breastmilk of 13 mothers. In the group of four infants with some sort of bleeding the dioxin content was significantly higher than in the group of the other 10 infants.

It is plausible that these strong chemical enzyme-inducers interfere with quinone metabolism as is described in the rat hepatocyte. In a human infant with a low vitamin K intake in breastmilk, an increased quinone metabolism may lead to a vitamin K deficiency with a haemorrhagic diathesis.

The second problem in exclusively breastfed children is prolonged jaundice. This is not as easy to relate to PCBs and dioxins. Since the unconjugated bilirubin is elevated in this prolonged jaundice, a form of increased haemolysis or inhibited conjugation must be taking place. Defects in synthesis, metabolism and transport of bilirubin may explain unconjugated hyperbilirubinaemia. Breastmilk jaundice may result if bilirubin synthesis is elevated because of haemolysis or because of an increased turnover of other heme-proteins (erythrocyte precursors, cytochromes or myoglobin) as a result of ingestion of abnormal human milk. Mostly inhibited hepatic conjugation of bilirubin forms the basis for the explanation of breastmilk jaundice. However, the role of pregnane-3a,20-d-diol as an inhibitor of bilirubin conjugation remains unclear. The effect of PCBs and dioxin on porphyrin metabolism in the liver cells is well known.

Uroporphyrinogen decarboxylase is inhibited and as a result ALA-synthetase is increased. In infants of mothers with Yusho disease a hyperbilirubinaemia is described, in combination with hepatomegaly.

In our opinion a causal relationship between PCBs, dioxins and furans, and vitamin K deficiency and late haemorrhagic disease is plausible. There is also a possible relationship with prolonged jaundice in breastfed infants, but this requires further study.

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