

Dioxins and innate immunity in the neonatal period and in adolescence in the Netherlands.

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Introduction:

In 1977 Kees Olie published on dioxins in fly-ash¹. In 1984 Gunilla Lindstrom found dioxins in her breastmilk. In 1986 Martin van den Berg published on dioxins in human breastmilk in the Netherlands². In 1987 a prospective study is started in the region of Amsterdam-Zaandam to effects of prenatal and lactational exposure to dioxins³. This mother-child cohort was studied in the neonatal period, at the age of 2 years, at the age of 7-12 years and at the age of 14-19 years. In the different periods, when the children were controlled, effects on immunology were studied. There are not many data in humans on dioxins and PCBs and innate immunity. Therefore the different findings in immunology in the Amsterdam-Zaandam cohort are summarized and related to other studies with immunologic data and to levels of dioxins in humans on the moment in Europe.

Materials and methods:

In 1987-1991 the Amsterdam-Zaandam cohort was started and exposure to dioxins was measured in breastmilk, collected in the first weeks of life as a measure of prenatal exposure. Postnatal- or lactational exposure is the amount of dioxins consumed by breastfeeding. The cohort was selected on a pregnancy and birth-weight optimality. In 1990-1991 immunologic data were collected at 7 days (n=18) and at 2 months (n= 26) by controlling the number of leucocytes and the differentiation and the number of thrombocytes and related to prenatal- and postnatal dioxin exposure.

In 1998, when the children were between 8 years old, again immunologic data, both data on the number of leucocytes and differentiation and thrombocytes were collected in combination with the thrombopoietin levels and related to prenatal – and postnatal dioxin exposure (n= 27).

In 2005, when the children were between 14-18 years old again immunologic parameters were controlled (n=33), number of leucocytes and differentiation and the number of thrombocytes and thrombopoietin levels were studied. In the serum levels PCDD/Fs and dl- PCBs were measured together with 8 lower brominated PBDE's. The immunologic parameters were related to the perinatal dioxin exposure and to the current exposure to dioxins and dl-PCBs (dioxinlike-PCBs) and PBDE's.

In 2014 five adults were controlled for their levels of dioxinlike compounds with the DR-CALUX method in the neighbourhood of Harlingen, a city in the north of the Netherlands, because people were concerned since a new incinerator started in that city. Eggs of farms in the neighborhood had high levels of dioxins up to 10 pg total TEQ (PCDD/Fs and dl-PCBs, mainly dioxins but sometimes high dl-PCBs). Because of this finding and the rumor that eggs from hobby farmers in general have high levels of dioxins, in a location in the middle of the Netherlands Nijkerk the eggs were also measured together with supermarket eggs as a control with help of the DR-CALUX method.

Results and Discussion:

In the neonatal period at 7 days of life a significant lowering of the number of granulocytes were found in relation to the prenatal dioxin exposure (n=18). The dioxin levels were between 8.7 and 62.7 ng ITEQ /kg milk fat. At 2 months the thrombocytes were decreased in association with the postnatal dioxin exposure (n=26). The postnatal cumulative dioxin intake varied from 5.7 –123.7 ng ITEQ⁴ .

In another study in the same period in the Rotterdam region the same finding of a lower granulocyte number now together with a lower monocyte number was found when the children were 3 months old, associated with both prenatal-and postnatal PCB/dioxin levels⁵. The mean total ITEQ levels, a combination of the dioxin levels and the dioxinlike PCBs levels were: 64.2 ng/kg fat (n=19).

In 1998 when the children of the Amsterdam-Zaandam cohort were 8-12 years old a significant decrease in the number of thrombocytes was found in relation to postnatal dioxin exposure, a decrease that was inversely related with thrombopoietin, a protein made in the liver and involved in the control of the number of thrombocytes. This indicates a defect at the production level, probably at the stem cell level. At this age it is possible that effects of a higher lactational exposure are persisting⁶ . In the Rotterdam study at the age of 3,5 years an effect on the number of middle ear infections is described in relation to the current sum of 4 PCBs (118, 138,153,180) mean level = 0.75 microgram/L plasma, but not an effect on the number of granulocytes. Thrombocytes are not measured⁷ .

In 2005 the Amsterdam-Zaandam cohort was again studied when the children were at the age of 14-18 years in their adolescence . Dioxin and Dioxin-like PCBs were measured in their serum together with 8 lower brominated PBDEs. In 33 adolescents serum levels of 4.4 (resp. 2.2 pg PCDD/Fs and 2.2 pg dl-PCBS) total WHOTEQ/g fat serum with a range of respectively 0.8-6.1 PCDD/Fs and 0.6-7.8 dl-PCBs. Levels of the 8 PBDE's were in adolescence : mean: 13.9 ng/g lipid with a range of 4.9-73.6 ng⁸ . A significant negative effect (P= 0.021) on the number of granulocytes was again found in relation to the current dl-PCB levels in the adolescents of the Amsterdam-Zaandam cohort .

PBDE's became a problem after 1990 in the Netherlands and didn't play a role when the children of our cohort were born. PBDEs as measured in 2005 in adolescents of our cohort had a negative effect on the adaptive immunity. A significant lower lymphocyte number was seen with the sum of the PBDEs, the main contributors were the PBDE congeners 183 (p=0.008),154 (p=0.009) and 85 (p= 0.03)⁹ .



Granulocyte = polymorphonuclear leucocyte= neutrophil.

The granulocyte is a leucocyte that belongs to the innate immunity, it is also named polymorphonuclear leucocyte or neutrophil. Innate immunity forms the first line of defense against micro-organisms by phagocytosis and is very important in the lungs and the intestines, because these tissues are under a constant threat of micro-organisms. Monocytes, natural killer cells, macrophages and thrombocytes belong to the innate immune system. This system doesn't have a memory in contrary to the adaptive immunity. In the third edition of Arnold Schecter's book: Dioxins and Health, Organohalogen Compounds Vol. 76, 728-731 (2014) 729

2012 chapter 6 pages 172-78 a good review of innate and adaptive immunology is described. The innate immunity together with the intestinal microbiota seem to play a role in the development of type I Diabetes¹⁰ (5) .

Thrombocytes are well known because of their clotting capabilities, but they are also an important part of the innate immunity. And often they are the first ones to decrease when an attack of bacteria or fungi takes place.

In conclusion we found negative effects on the innate immunity (granulocytes and thrombocytes) perinatally at rather high background levels of dioxins, at prepubertal age on thrombocytes and in adolescence again with dioxinlike PCB levels on the number of granulocytes. Even with the rather low current levels of dioxinlike PCBs a negative effect on the innate immunity is seen.

Situation in the Netherlands:

Not many data are available in the Netherlands on current levels of Dioxins and Dioxinlike PCBs in the population. What we have is: 1. the adolescent levels of a total dioxin WHOTEQ of 4.4 with a range of 1.4 – 13.9 WHOTEQ pg/g fat serum. And 2. levels in blood of 5 adults in the region of Harlingen in 2014 measured with DR-CALUX: 10, 23, 25, 28, 108 total PCDD/Fs and dl-PCBs/g fat serum . Four people have levels normally found in Western Europe, the last one has a very high dl-PCBs level. He has cancer of the prostate. The levels measured with the DRCALUX are comparable with the ones measured with the GC-MS.

The situation in the Netherlands of dioxin levels in human beings is not worse in comparison to the levels found in cord blood and in maternal blood in 5 other European countries, England, Norway, Greece, Spain, Denmark with a median level of 34.2 (range 10-156) total TEQCALUX /g fat in cord serum and 38.3 (in the period 2006-2010 : range 6-129) in blood of the mothers¹¹ (6) . These levels are supposed to be low according to the authors.

Eggs:

In a city in the North of Holland named Harlingen a new incinerator was started in 2009 and people were concerned about health effects. Eggs from hobby farmers in the neighborhood were tested and some had high levels up to 10 total WHOTEQdioxin/g fat.

Eggs from wild birds (tapuit and graspiepers) that breed in the Dunes or in a Natural Park in the North of Holland have 20 times higher levels of dioxins than the hobby eggs and concentrations go up to 200 TEQ dioxin/g fat in the eggs. Their population is sharply lowered after 1970 from thousands to only 250-290 pairs. The embryo's showed typical congenital malformations as is seen after intoxication with dioxins and 30 % of the eggs don't come out of the shell. The food of these birds are insects that live in the upper layer of the Dutch ground. (Information Stichting Bargerveen).

Eggs from Nijkerk in the middle of Holland from a local hobby farm contained 2.0 TEQCALUX pg/g fat, mainly PCDD/Fs. But eggs (not organic and produced by chickens living in mega factories) in Holland were very low in dioxin level. In 2013 David Mortimer showed the levels of dioxins in different foodstuffs and besides the known vulnerable ones like fish and dairy products also the item "sugar and preserves" was rather high for both the chlorinated and brominated compounds. This item includes all sorts of sauces like pasta sauce and pesto sauce and dip sauces and pudding¹² .

Looking at these laboratory data of the innate immunity it must be concluded that the current levels of dioxin in people in Western Europe are too high. The local food is now too often not controlled at all. That is an important item since it is becoming more and more popular to eat locally produced food. Further on it looks that the surface of the ground of the Netherlands in general should be mistrusted.

Conclusion:

The levels of dioxins and dioxinlike compounds in the population in Western Europe on this moment are too high and give rise to a negative effect on the innate immunity. Considering the importance of the innate immunity, the control of food for dioxins and dioxin-like compounds must be better. Especially local produced food should be better controlled. Further spread of dioxins and dioxinlike PCBs must be prevented.

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