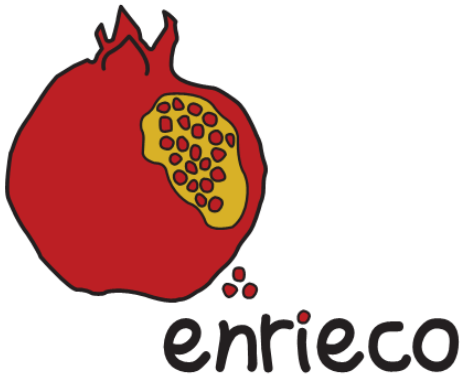
The ENRIECO Project:

ENVIRONMENTAL HEALTH **R**ISKS IN **E**UROPEAN BIRTH **CO**HORTS



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Report

Persistent Organic Pollutant (POP) Case Study

Modelling exposure–response associations between maternal PCB serum levels and birth weight: a META-analysis within European birth-cohorts

Work Package 3

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Persistent Organic Pollutant (POP) Case Study: Modelling exposure–response associations between maternal PCB serum levels and birth weight: a META-analysis within European birth-cohorts

Summary

Exposure to high concentrations of POPs may cause fetal toxicity as seen from accidental exposures, but the effects at lower concentrations are not as obvious. Large scale-studies with a sufficient number of participants in well-defined groups with substantial exposure contrast are needed in order to fully elucidate the possible adverse effects of persistent organochlorines on human reproductive health. The ENRIECO framework provides the basis for such a study. The overall aim of the case-study is to prove the ENRIECO concept by an examination of the feasibility using European mother-child cohorts to obtain additional insight into environmental effects on reproductive outcomes.

European cohorts with available data on Persistent Organic Pollutants have been identified and contacted and a common protocol detailing study variables, data harmonization and statistical analysis was developed and updated during 4 international workshops held during 2010. The study focuses on one specific congener of the PCB family, CB-153, and on p,p-DDE (metabolite of the insecticide DDT) as markers of POP exposure regardless of matrix (cord blood, maternal serum or breast milk). The health outcome considered is birth weight adjusted for duration of pregnancy.

Statistical analyses based upon uniform software code have been performed on data from 12 cohorts including some 7.300 mother-child samples with biological measures of POP exposure. At this stage the meta-analysis is expected to be performed during October-December 2010.

In conclusion, European birth cohorts provide in aggregate a unique research resource that can and should be exploited to obtain added value for research objectives that requires large datasets. The ENRIECO POP-case study proves this concept by its analyses of some 7300 mother-child pairs with individual measures of contaminant exposure levels in blood. Results of the meta-analysis are submitted for publication in an international biomedical journal by January 2011.

Background and context

Objective. The overall aim of the case-study is to prove the ENRIECO concept by an examination of the feasibility using European mother-child cohorts to obtain additional insight into environmental effects on reproductive outcomes. The case-study will evaluate the additional value of meta-analyses or pooled analyses across several European birth cohorts relative to stand-alone analyses.

The specific objective is to model exposure response associations between biological markers of POP-exposure to selected adverse pregnancy outcomes in order to

Discuss causal inference
Detail dose-response relations, if any
Identify thresholds and no-effect levels, if any
Identify vulnerable subgroups, if any
Examine interactive effects of exposures and characteristics

Background. Persistent organic pollutants (POPs) are organic compounds that are highly resistant to environmental degradation with half-lives in the environment and in living organism in the range of several years. POPs bioaccumulate in fat tissues in the organism and biomagnify through the food chain from lower organisms to top predators including humans. An important class of POPs are organochlorines that include a number of anthropogenic compounds manufactured in large scale since 1930s. The most widespread organochlorines in the environment and in human tissues are polychlorinated biphenyls (PCB) and dichlorodiphenyltrichloroethane (DDT). The concentration of these compounds and several other organochlorines as chlordane, aldrin, dieldrin, hexachlorobenzene, toxaphene and dioxins are highly correlated in serum samples from the general human population and exposure to the most common PCB-congener (CB-153) has therefore been suggested as an indicator of overall exposure to persistent organochlorines [1-3]. The co-occurrence of these compounds in human samples makes it difficult to establish which compounds that cause the observed effects. Moreover, one group of organochlorines, the dioxins, is more toxic than most PCB-congeners and has the same mechanisms of action as the co-planar PCB-congeners.

The production of PCBs and DDTs has been limited or completely banned since 1970s in most developed countries. The last PCB-production facility in Russia, was shut down in 1993. In spite of this, organochlorines including PCBs are still being released into the environment from previously produced material or by combustion processes.

The concentration of PCBs in human tissues has decreased since the ban of these compounds in most countries. During the past 10 years the decrease has levelled off. Compounds are still detected in blood and milk samples in the vast majority of humans all over the globe.

Concern about adverse reproductive effects of POPs including PCBs arises from experimental studies and accidental exposure of humans. Moreover, during the past few years several observational studies have addressed reproductive toxicity of POPs in exposed population and using hospital based case-referent studies. These studies indicate that high concentrations of persistent organochlorines may adversely affect semen quality and cause testicular cancer, induce menstrual cycle abnormalities and spontaneous abortions and cause delayed pregnancy, reduced birth weight, skewed sex ratio and altered age of sexual development[4]. Most effects have been demonstrated at exposure levels above the present exposure level in European and North American populations.

An overview of epidemiological studies investigating effects of the persistent organochlorine on birth weight is given below based on [4]

Table 1:

Reference and Place	Exposure groups/ compounds	Mean, median or midrange estimated as maternal serum PCB or DDE[a]	Birth weight
[5] Michigan, USA	Fish eaters – PCBs	5.5 ng/g	↓
[6] New York State, USA	Working women exposed to PCB	21 ng/g	↓
[7] Wisconsin, USA	Fish eaters (PCBs)	2.8 ng/g	↑
[8] Taiwan	PCB, PCDF maternal exposure	-	↓
[9] Sweden	Fishermen's wives East coast (high PCB) vs West coast (lower PCB)	-	↓
[10] Sweden	East coast fishermen's wives High vs low fish consumption Living in fishing village	-	↓ ↓
[11] The Netherlands	General population (PCBs)	1.6 ng/g	↓
[12] Sweden	East coast fishermen's wives CB-153 estimated in blood >300 ng/g lipid in plasma	3.4 ng/g	↓
[13] Rural Finland	General population PCDDs + PCDF PCB	5.9 ng/g	↓ →
[14] USA	p,p'-DDE increasing concentrations	25 ng/g	↓
[15] Faroe Islands	Fishing community (PCB)	2.2 ng/g	→
[16] India	General population (p,p'-DDE) HCHs other DDTs	7.6 ng/g	↓ ↓ →
[17] Ukraine	General population (DDE, PCB	16.4 ng/g DDE 4.0 ng/g PCB	→

[a] Values approximated by conversions – see Toft et al 2004 for details.
→ no effects on birth weight
↓ significant decrease in birth weight.
↑ significant increase in birth weight

The studies indicate consistently, that pregnant women exposed to relatively high concentrations of PCB or DDT are in increased risk of giving birth to children with low weight. Besides studies of women with accidental exposure to high concentrations of PCBs in Taiwan and Japan and a large US study of women giving birth between 1959 and 1966 (when DDT was still being used) found a close response relationship between DDT-concentration in maternal serum on the one hand and low birth weight on the other hand. Children in the high exposure group (> 60 ng/g) weighed 150g less and were born about one week earlier than the children in the low exposure group (< 15ng/g).

However, at lower exposure level findings are not entirely consistent (cf. table). One reason that some studies may fail to demonstrate an association between PCB-exposure and birth weight, if such effect really do exist, may be lack of adequate exposure contrast. All humans have measurable concentrations of POPs in their serum and a no-exposure group cannot be defined.

In summary, exposure to high concentrations of POPs may cause fetal toxicity as seen from accidental exposures, but the effects at lower concentrations are not as obvious. Therefore, a recent review concluded that "large scale-studies with a sufficient number of participants in well-

defined groups with substantial exposure contrast are needed in order to fully elucidate the possible adverse effects of persistent organochlorines on human reproductive health" [4]. The ENRIECO framework provides the basis for such a study.

Methodology

Study populations. European cohorts with available data on Persistent Organic Pollutants have been identified and contacted (Table 2), and a common protocol detailing study variables, data harmonization and statistical analysis was developed (Annex 1) and updated during 4 international workshops held during 2010 (minutes available on request). Among others, the choice was made to focus on one specific congener of the PCB family, CB-153, and on p,p-DDE (metabolite of the insecticide DDT) as markers of POP exposure regardless of matrix (cord blood, maternal serum or breast milk). The main health outcome in focus will be birth weight adjusted for duration of pregnancy. Altogether some 7300 mother child pairs with POP measurements in 12 cohorts were included.

The detailed study protocol specifying variables (background characteristics, exposures, outcomes and extraneous variables) and the analytical design was translated into statistical software code (SAS and SPSS) thus enabling each center to run uniform statistical analyses in their own cohort without transfer of individual data across country borders. One centre has taken responsibility of aggregating statistical output into summary tables and to prepare the meta-analysis based upon cohort specific adjusted regression coefficients of birth weight on cord serum POP concentration. At this stage the meta-analysis is expected to be performed during October-December 2010.

Exposure Assessment. The lipid adjusted serum concentration of CB-153 is taken as an indicator of organochlorine exposure level. The appropriateness of using CB-153 as an indicator of total PCB- exposure has been demonstrated in Swedish and Inuit populations [1,3] In so far as several PCB congeners have been measured, it is essential to examine if the PCB-congener profiles are comparable across populations. If not, major categories of PCB-exposure profiles is defined and analyses stratified accordingly. This work is currently on-going. If available, the serum concentrations of n-3 fatty acids or proxy indicators of fish/sea mammal intake are also included to characterise exposure profiles. Fish eaters may have high concentrations of POPs as well of n-3 acids and adverse effects of POPs on birth weight might be counteracted of effects of n-3 fatty acids. The time in pregnancy when a serum sample is taken may systematically interfere with the concentration of POPs and therefore time in relation to gestational age is accounted for in analyses. To obtain comparable measures of POP exposure levels across populations conversion factors were developed based upon cohorts with information on concentration in several matrices.

Serum concentrations of PCBs and the DDT-metabolite p,p-DDE are highly correlated in some populations as Inuits and Swedish fishermen-families [18], but not in other populations depending on dietary habits and local contamination. Separate analyses of p,p-DDE is performed when appropriate.

Preliminary exposure data across cohorts are provided in Tables 3-4.

Outcomes. The main outcomes to be examined are duration of gestational age and weight at birth in pregnancies that are carried to gestational week 22 or beyond. Only singleton pregnancies are included. The methods for detection of gestational age need to be taken into account. When alternative methods have been used, priority is given to first day of last menstrual period, ultrasound measurements and others in that order. Sex ratio at birth is an additional outcome that may be considered.

Covariates. Potential confounding and/or interacting factors that are accounted for in the analysis include maternal age, gestational duration (for birth weight analyses) parity, pre-pregnancy height and body mass index, socio-economic status, gender, tobacco smoking during pregnancy, intake of alcohol beverages during pregnancy and chronic disease.

Data analyses. The defining criteria and formats for exposure variables, outcome variables and covariates are harmonised according to a uniform protocol and a protocol describing the analysis step by step is to be developed. The initial analysis is to be formed separately for each study cohort – either by the principal investigator and his/her team or by a small group of researchers assigned by the project group.

The birth weight as continuous and dichotomous outcome is modelled as a function of CB-153 and covariates using linear and logistic regression. Cut-offs defining dichotomized variables have been agreed upon before analyses were carried out. Several options are available for treatment of confounders. If all covariates are included in initial full-models and eliminated according to change of estimate principles [19], different set of confounders will probably be included in analyses performed by centre. Therefore it was decided to keep certain variables that are believed to be of particular importance in the models irrespective of change of estimates across all centres. Associations are also modelled by non-parametric graphical methods. Formal analysis of exposure or response by trend analysis and analysis for thresholds are performed if appropriate.

Heterogeneity of estimates across the birth cohorts is examined and test for heterogeneity are performed by standard methods. If appropriate, aggregated data is analysed either by analysing summary statistics from each birth cohort (meta-analysis) or by stratified analysis of a pooled dataset including all observations from all cohorts. The latter is to be decided during the mid-term workshop.

Possible effect modifications by POP exposure profile, gender and smoking have also been investigated.

Current work in the European birth cohorts

Not applicable for this WG

Recommendations

European birth cohorts provide in aggregate a unique research resource that can and should be exploited to obtain added value for research objectives that requires large datasets. The ENRIECO POP-case study proves this concept by its analyses of some 7300 mother-child pairs with individual measures of contaminant exposure levels in blood.

Meta-analyses of birth cohort data collected in different countries can be performed by centralized analyses of either raw data or summary output from each cohort. Each of these approaches has according to the experience of working group pro's and cons.

It speaks in favour of meta-analysis based upon summary output from each cohort (the approach chosen by the POP case-study working group) that this approach

bypasses barriers for transfer of full datasets across borders
deeply involves all principal investigators and provides a better understanding of the data
enables consensus agreements on key analytical decisions before analyses
promotes trustbulding, ownership, learning and enjoying
promotes sharing of research tools with other research groups

Major con's are that this approach obviously is more labour and time consuming and is less efficient and flexible than centralized analyses of raw data by a small research group

It is recommended that the participatory benefits of decentralised analyses is accounted for in future data analyses where a small group of researchers have access entire datasets whenever this is legally and ethically possible.

Dissemination

A paper is currently being prepared for this case study;
Birthweigth according to maternal serum levels of PCB-153 and p,p-DDE: a meta-analysis of elleven European birth cohort studies. Govarts E et al and ENRIECO.

We intend to submit the paper in January to the first priority of journal - *Environmental Health Perspectives.*

Annex I - References

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Annex II – Tables

Table 2 Overview of cohorts providing data for the ENRIECO POP CASE study, October 2010

Cohort	Region (Country)	Newborns	Time period (recruitment (child birth))	Matrix	PCB153	p,p'-DDE
ARC-RISK	Russia Tromso (Norway)	900	2009-2010			
DUISBURG	Duisburg (Germany)	196	2000-2002	Maternal blood	196	189
ELFE pilot	(France)	44	2007	Breast milk	44	/
FAROESI FAROESIII	The Faroe Islands	1022 547	1986-1987 1998-2000			
FLEHSI	Flanders (Belgium)	1196	2002-2004	Cord blood	1068	1114
GRD	Groningen (The Netherlands) Rotterdam (The Netherlands) Dusseldorf (Germany)	588	2000-2002	Cord blood	523	/
HUMIS	Norway	2327	2003-2008	Breast milk	418	418
INMA	Ribera Ebre Menorca Granada Valencia (Spain) Sabadell Asturias Gipuzkoa	3400	1997-2008	Cord blood Cord blood Cord blood Cord blood Maternal blood Cord blood Maternal blood	70 404 / 499 (2202) 602 25 602	70 404 318 499 (2520) 602 25 602
INUENDO	Greenland Warsaw (Poland) Kharkiv (Ukraine)	546 199 589	2002-2004	Maternal blood Maternal blood Maternal blood	546 199 589	546 199 589
Michalovce	Slovakia	1160	2001-2004	Cord blood	1082	1082
PELAGIE	Brittany (France)	396	2002-2006	Cord blood	394	319
RHEA	Greece	1500	2007-2008	Maternal blood		

Table 3 Overview of CB-153 exposure levels across POP case study cohorts, October 2010

Cohort	Region	N	Mean	Std	Median	Min	Max	P10	P90	LOD LOQ*	LOD LOQ*[2]	N <LOD (%)	Original matrix
ARC-RISK													
DUISBURG		196	73.2	49.2	62.0	3.2	480.0	28.0	126.0	5 ng/L	1 ng/L	0	Maternal blood
ELFE pilot		43	75.3	39.5	69.4	14.9	200.3	35.0	125.6	0.885 ng/g fat	0.80 ng/L	0	Breast milk
FAROES		167	648.5	579.9	484.2	14	4877	173.1	1302.2	400 ng/L	80 ng/L	2 (1.2%)	Maternal blood
FLEHSI		1015	73.3	56.7	60.0	14.1	450.0	14.1	144.0	20 ng/L	20 ng/L	202 (19.9%)	Cord blood
GRD		523	170.6	99.7	150.0	10.0	850.0	80.0	280.0	10 ng/L	10 ng/L	0	Cord blood
HUMIS		409	32.3	15.0	29.4	6.6	141.0	17.3	48.4	0.458 ng/g fat	0.41 ng/L	0	Breast milk
INMA		2144	115.2	107.5	88.6	10.0	1438.4	28.3	232.5	32.4-200 ng/L	14.2-200 ng/L	209 (9.7%)	Cord blood & Maternal blood
INUENDO	Greenland	546	253.8	341.9	155.1	7.1	4470.0	50.0	543.5	50 ng/L	10 ng/L	7 (1.3%)	Maternal blood
	Warsaw	199	23.8	17.8	20.1	7.1	114.5	7.1	43.3	50 ng/L	10 ng/L	43 (21.6%)	Maternal blood
	Kharkiv	577	45.8	36.3	37.1	7.1	500.5	16.0	82.5	50 ng/L	10 ng/L	20 (3.5%)	Maternal blood
Michalovce		1036	393.5	458.3	271.8	4.04	6388.6	101.2	776.0	3.4-23 ng/L	3.4-23 ng/L	2 (0.2%)	Cord blood
PELAGIE		394	126.7	77.4	110.0	17.0	730.0	57.0	210.0	10 ng/L	10 ng/L	0	Cord blood
RHEA		30	28.0	13.4	23.8	9.3	60.9	13.7	52.9	4 ng/L	0.8 ng/L	0	Maternal blood

Table 4 Overview of p,p-DDE exposure levels across POP case study cohorts, October 2010

Cohort	Region	N	Mean	Std	Median	Min	Max	P10	P90	LOD LOQ*	LOD LOQ*²	N <LOD (%)	Original matrix
ARC-RISK													
DUISBURG		189	186.1	250.4	124.2	29.9	2093.0	57.5	345.0	5 ng/L	1.15 ng/L	0	Maternal blood
ELFE pilot		-	-	-	-	-	-	-	-	-	-	-	-
FAROES		167	1964.5	1649.0	1389.2	336	11462	553.2	4299.6	400 ng/L	80 ng/L	0	Maternal blood
FLEHSI		1061	315.6	344.6	220.0	14.1	3740.0	73.3	620.0	20 ng/L	20 ng/L	19 (1.8%)	Cord blood
GRD		-	-	-	-	-	-	-	-	-	-	-	-
HUMIS		409	69.0	102.1	45.8	6.6	1413.3	22.0	122.2	0.224 ng/g fat	0.25 ng/L	0	Breast milk
INMA		2431	992.7	2000.9	353.5	11.5	29970.4	92.6	2491.6	19-500 ng/L	16.33-500 ng/L	64 (2.6%)	Cord blood & Maternal blood
INUENDO	Greenland	546	729.8	786.8	501.1	16.3	6152.5	141.4	1579.5	100 ng/L	23 ng/L	10 (1.8%)	Maternal blood
	Warsaw	199	948.4	596.0	769.1	52.0	4213.6	369.2	1648.6	100 ng/L	23 ng/L	0	Maternal blood
	Kharkiv	577	1265.9	876.7	1053.7	223.7	8429.5	542.8	2149.5	100 ng/L	23 ng/L	0	Maternal blood
Michalovce		1036	1329.5	1338.4	1014.7	2.9	20575.4	321.5	2655.1	1.3-13 ng/L	1.3-13 ng/L	8 (0.8%)	Cord blood
PELAGIE		319	305.2	354.5	210.0	50.0	3300.0	100.0	490.0	20 ng/L	20 ng/L	0	Cord blood
RHEA		30	659.2	447.6	570.4	158.2	2038.5	221.8	1266.6	5 ng/L	1.15 ng/L	0	Maternal blood