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Extramural Research

2003 Progress Report: Children's Vulnerability to Environmental Immunotoxicant Exposure

Research Project Search

NCER Research Project Search

EPA Grant Number: R830758
Title: Children's Vulnerability to Environmental Immunotoxicant Exposure
Investigators: Grandjean, Philippe , Weihe, Pal
Institution: Harvard School of Public Health
EPA Project Officer: Deener, Kacee
Project Period: May 5, 2003 through May 4, 2006 (Extended to May 4, 2007)
Project Period Covered by this Report: May 5, 2003 through May 4, 2004
Project Amount: $750,000
RFA: Children's Vulnerability to Toxic Substances in the Environment (2002)
Research Category: Children's Health , Health Effects , Human Health

Description:

Objective:

The objective of this research project is to determine the immunotoxic risk in children exposed prenatally and postnatally to polychlorinated biphenyls (PCBs). Experimental animal studies with Aroclor 1254 used by the U.S. Environmental Protection Agency for calculating a Reference Dose (RfD) for PCBs suggest that immunotoxicity may be critical, but current exposures, especially those from breast-feeding, greatly exceed the RfD.

Progress Summary:

The project was started as planned, and the approved protocol has been followed without any changes needed. The procedures of contacting subjects, informed consent, blood sampling, and clinical examination have not deviated in any way from the approved grant proposal. By mid-2004, the birth cohort followup achieved the following accomplishments:

- 530 mothers and their children (including pilot subjects) have received invitations by letter to participate in the 5-year examination, and a total of 480 have accepted and completed the examination.
- 10 parents wished to withdraw from the cohort study without any particular reason given (we do not demand any explanation). In addition, seven parents do not intend to participate in this part of the study because of the sensitive age of the child, but they do want to participate again when the child has reached school age.
- 18 children emigrated with their families to Denmark, three to Iceland, and one each emigrated to the United Kingdom, Spain, and Greenland.
- In regard to the cohort proper, a total of 392 cohort children have been examined, thus leaving slightly less than 150 for the remainder of the project.
- In regard to the completion of clinical procedures during these examinations, 459 blood and hair samples were obtained before vaccination, and 314 blood samples were obtained 4 weeks after vaccination. These numbers include pilot subjects. The samples currently are stored and awaiting chemical analysis.

We received approval to continue our project from the Harvard School of Public Health's Human Subject's Committee and, therefore, are in compliance with Federal and school regulations for conducting research with humans. Biological samples are being collected and handled in accordance with the guidelines from the Faroese Labor Inspection (similar to Occupational Safety and Health Administration guidelines).

As examinations have just begun, there have been no results to date. Additionally, no data results or evaluations were made during Year 1 of the project because data collection is still ongoing.

Future Activities:

We will recruit and examine the remainder of the study cohort in Year 2 of the project, with additional studies (especially analyses of antibodies and exposure biomarkers) being initiated, as outlined in the grant proposal.

Journal Articles:
No journal articles submitted with this report: View all 3 publications for this project

Supplemental Keywords:

cumulative effects, dioxin, dose-response, epidemiology, human health, hypersusceptibility, infants, marine food contamination, methylmercury, mixed exposure, prenatal exposure delayed response, risk assessment, sensitive populations, polychlorinated biphenyls, PCBs, blood samples,, HUMAN HEALTH, ENVIRONMENTAL MANAGEMENT, INTERNATIONAL COOPERATION, Scientific Discipline, RFA, Health, PHYSICAL ASPECTS, Risk Assessment, Risk Assessments, Health Risk Assessment, Physical Processes, Children's Health, Biochemistry, Environmental Policy, Exposure, exposure assessment, exposure model, health effects, developmental effects, developmental toxicity, immunotoxicology, children's environmental health, prenatal exposure, post-natal exposure, dietary exposure, pesticide exposure, pesticides, vulnerability, pregnant women, PCB, children's vulnerablity, Human Health Risk Assessment, polychlorinated biphenyl

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Progress Summary:

The project was started as planned, and the approved protocol has been followed without any necessary changes. Thus, the procedures for contacting subjects, informed consent, blood sampling, and clinical examination have not deviated in any way from the approved grant proposal. To date, the birth cohort followup for Year 5 is complete and has achieved the following accomplishments:

- The project cohort includes a total of 549 children who had a nitric-oxide synthase (NOS) examination at 2 weeks of age and data on mercury and persistent organic pollutants (POPs) exposure at birth.
- At age 5 years, 501 of the children participated in the follow-up examinations (91.3%).
- We obtained a blood sample (before vaccination) from 485 of the cohort members (88.3%).
- We subsequently obtained a blood sample 4 weeks after vaccinations from 398 of these children (82.1%).

The reasons provided (by the total of 48 nonparticipants) for not participating in the followup include:

- Moved to Denmark (20)
- Moved to Iceland (2), Greenland (1), and Spain (1)
- Retracted from the study, no reason revealed (14)
- Did not want to participate in the 5-year examination, though perhaps later on (8)
- Did not respond to the invitation letter (1)
- Fear of needles (1)

The hair samples have been transferred to the analytical laboratory in Denmark, and mercury analyses have been initiated. Vials from the first examination have been transferred to the analytical laboratory, which will conduct the antibody measurements. Antibody assessments have not yet begun because of the lack of capacity at the immunology laboratory. The same applies to the PCB analyses. Stored maternal pregnancy serum for arylhydrocarbon receptor activation assays has been transferred to the laboratory at Boston University, and the analyses have been initiated. Sample storage is otherwise maintained in the Faroes.

Although no results can be reported at this early stage, the project is moving forward as anticipated in accordance with the time schedule. The participation rates are considered highly satisfactory.

We recently received approval for continuation of our project through age 7 years from the Harvard School of Public Health's Human Subjects Committee.

Future Activities:

Year 2 of the research project has been devoted to recruiting and examining the second half of our cohort, with additional studies (especially analyses of exposure biomarkers) being initiated, as outlined in the grant proposal. We will analyze the complete set of serum samples for specific antibodies and for PCBs during the following year. Data analysis will include careful evaluation of potential confounders (which are not expected to be of major importance) as outlined in the grant proposal, with bivariate associations, multiple regression analyses, and structural equation models.

Journal Articles:
No journal articles submitted with this report: View all 3 publications for this project

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Progress Summary:

The research project was started as planned, and the approved protocol has been followed without any necessary changes. Thus, the procedures of contacting subjects, informed consent, blood sampling, and clinical examination have not deviated in any way from the approved grant proposal. To date, the birth cohort followup for age 5 is complete and has achieved the following accomplishments:

The total cohort was comprised of 656 Faroese children (including seven sets of twins), 547 of which were funded by EPA as the main cohort, who had a nitric oxide synthase examination at 2 weeks of age, and also had data on mercury and persistent organic pollutant (POP) exposure at birth. (Additional funds for the other children were provided by the Arctic Environment Program and the Danish Environmental Protection Agency.)

At age 5 years, 505 of the main cohort children participated in the follow-up examinations (92%). We obtained a blood sample (before vaccination) from 485 of these cohort members (88%). We subsequently obtained a blood sample approximately 4 weeks after vaccinations from 398 of these children (82%).

In total, we were able to draw blood from 557 of 594 participating children. These results are quite satisfactory. Some of the children and their parents decided in advance not to take the blood test, but this was after they underwent the examination. Others decided not to take the blood test at the time of the examination; we tried but did not succeed to draw blood after first and sometimes repetitive tries, despite the best efforts of the technician.

The reasons for not participating in the followup (for the total of 42 nonparticipants of the main cohort) are:

- Moved to Denmark (18).
- Moved to Iceland (1) and Spain (1) .
- Retracted from the study, no reason revealed (13).
- Did not want to participate in the 5-year examination, though perhaps later on (8).
- Fear of needles (1).

At the second follow-up examination, blood tests were done at about 4-6 weeks subsequent to the scheduled 5-year vaccinations. In this case, we succeeded to get blood samples from 458 cohort members.

In connection with the first blood test, we aimed at securing 30 mL of blood from the children:

- 5 mL of blood was for mercury analysis.
- 5 mL of whole blood was for hematological examination.
- 2 mL serum was for POP analysis.
- 1 mL serum was for vaccination antibody response.
- 1 mL serum was for IgE.
- 2 x 2 mL was for C-reactive protein, IgA–M, albumin, bilirubin, tryglycerides, and cholesterol.

We also obtained a hair sample for mercury analysis.

With the second blood test, we took only 5 mL of blood in a single vial, which, after centrifugation, revealed the 2 mL of serum needed for antibody concentration measurement.

Samples of blood and hair were transferred to the Department of Environmental Medicine at the University of Southern Denmark (SDU), and the results have been reported (Table 1).

Table 1. Hair and Blood Mercury Levels

60 months	N	Minimum	Maximum	Mean	Std. Deviation
Blood mercury	554	00	36.5	4.02	4.17
Hair mercury	580	89	9.48	2.10	1.24

These results are in accordance with expectation.

The PCB analyses at SDU have not yet been completed but are expected in August 2006.

Vials from the first examination have been transferred to the analytical laboratory at Statens Serum Institut, which will conduct the antibody measurements. These assessments have been delayed because of the lack of capacity at the immunology laboratory, but results should be completed in August 2006.

Stored maternal pregnancy serum for AhR activation assays has been transferred to the laboratory at Boston University, and the analyses have been initiated. Samples storage is otherwise maintained in the Faroes.

Although no results can be reported at this stage, the project is moving forward as anticipated in accordance with the time schedule. The participation rates are considered highly satisfactory.

The 7-year examination of Cohort 3 children for this project has been initiated (with support from the National Institute of Environmental Health Sciences). Although no project results can be reported at this stage, the project is moving forward as anticipated and in accordance with the time schedule for the clinical examinations, although delays have occurred, however, in the laboratory schedules. The participation rates are considered highly satisfactory.

There have been no publications to date in regard to this grant because data collection still is ongoing; however, the findings of the pilot study that were first outlined as preliminary data in the original application have been finalized for publication and will appear in *PLoS Medicine* in August 2006.

Future Activities:

The analyses of the serum samples for PCBs and for antibody concentrations will be completed. Data analysis will include careful evaluation of potential confounders (which are not expected to be of major importance) as outlined in the grant proposal, with bivariate associations, multiple regression analyses, and structural equation models. Letters have been sent to all members of the cohort, with information about the clinical results of the examinations at age 5 years and about the next stage of the project (7-year examinations). As a result, many children already are consented for the next stage of the project (supported by NIEHS).

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Type	Citation	Project	Document Sources
Journal Article	Heilmann C, Grandjean P, Weihe P, Nielsen F, Budtz-Jørgensen E. Reduced antibody responses to vaccinations in children exposed to polychlorinated biphenyls. *PLoS Medicine* 2006;3(8):e311. Abstract Available Full Text Available	R830758 (2005) R830758 (Final)	• Abstract from PubMed • Full-text: PLOS Journals Full Text EXIT Disclaimer • Other: PLOS Journals PDF EXIT Disclaimer

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Description:

Objective:

The main objectives of this project were to examine PCB-exposed cohort children at preschool age with sensitive chemical markers of immune function alterations, emphasizing specific antibody responses to protein vaccine challenges; to ascertain the prenatal and postnatal exposure profile for cohort children with regard to PCBs and other potential immunotoxicants from marine food; to apply a novel method to assess in vitro activation of the arylhydrocarbon receptor (AhR) as an integrated measure of dioxin-related PHAHs in serum previously obtained from the cohort mothers in late pregnancy; to determine the association of prenatal and postnatal PHAH exposure levels and AhR activation with immune function alterations; and to carry out appropriate statistical analyses, including determination of benchmark dose levels for major contaminants, their mixtures, and integrated exposure measures as predictors of immunotoxic effects.

Summary/Accomplishments (Outputs/Outcomes):

The total cohort was comprised of 656 Faroese children (109 of which were funded by The Arctic Environment Program and the Danish Environmental Protection Agency). The present part of the cohort had a Neurological Optimality Scale (NOS) examination at 2 weeks of age and also had valid data on mercury (cord blood and/or maternal hair) and PHAH (maternal serum and/or milk) exposure at birth.

According to the pediatric immunization schedule in the Faroe Islands (similar to Scandinavia), the children receive three vaccinations during the first year that include the tetanus and diphtheria toxoids. A booster is then given at age 5 years. In this community, the vaccinations are normally completed by all children. The present study aimed at exploring the specific antibody concentrations against the two toxoids just before the booster vaccination, with a repeat examination about one month later, as is the usual practice in vaccinology.

Of the 547 cohort children, 485 (88.7%) participated in the examination just before age 5 years. The loss to follow-up was mainly due to the family having moved abroad or the children being afraid of needles. However, from 20 of these children, serum for antibody analysis was not obtained. Some of the children or their parents had decided in advance not to participate in the blood test, while others decided at the time of the examination. The average age of the children at the time of examination was 4.96 years (s.d., 0.06). These examinations were carried out from March 2003 to January 2005. One child had to be excluded because the 5-year vaccination had already been performed prior to the examination.

With the first blood test we aimed at obtaining 30 ml of blood from the children:

- 5 ml of blood was for mercury analysis (completed)
- 5 ml of whole blood was for hematological examination (not done due to incomplete sampling)
- 2 ml serum was for POP analysis (completed)
- 1 ml serum was to track vaccination response (completed)
- 1 ml serum was for IgE (moved to age 7 years)
- 2 x 2 ml was for CRP, IgA-M, albumin, bilirubin, tryglycerides and cholesterol (moved to age 7 years)
- In addition, a hair sample for mercury analysis was taken from the occipital area (completed)

A total of 391 children (71.5% of total cohort) returned for the follow-up examination about one month after the booster vaccination. In four cases, enough serum for antibody analysis was not obtained. The average age of the children at the time of the second examination was 5.20 years (s.d., 0.13). The age range was wider, up to 5.84 years. The time from the booster vaccination averaged 35 days (s.d., 11), with a maximum of 77 days. Seven children were examined less than two weeks after the booster vaccination (and will be deleted from the statistical analysis). This variability was due to scheduling problems related to parental work obligations, incident disease, foreign travel, and similar problems. Some children were excluded from follow-up, because their 5-year vaccination had not yet been performed.

At the re-examination, only 5 ml of blood was taken in a single vial, so that, after centrifugation, 2 ml serum was available for antibody measurements (completed).

The hair and blood samples for contaminant analyses were transferred to the analytical laboratory in Denmark. The results for the pre-booster samples are:

Contaminant	Number	Geometric mean	50% range	Total range
Blood-Hg (µg/L)	462	2.67	1.36-5.44	0.03-36.5
Hair-Hg (µg/g)	485	1.86	1.32-2.47	0.89-9.48
Serum-PCB (µg/g lipid)	464	1.14	0.71-1.92	0.07-9.56
Serum-PCB teq (pg/g lipid)	464	1.24	0.75-2.24	0.1-12.2

The total PCB concentration was calculated as twice the sum of the concentrations of congeners CB-138, CB-153, and CB-180. In addition, the dioxin-equivalent concentrations

of major mono-ortho congeners CB-105, CB-118, and CB-156, was also calculated using WHO equivalence factors.

The increased level of exposure was thereby confirmed. The PCB concentrations are mainly due to the persistence of PCB transferred from the mother during pregnancy and during lactation. The mercury is due to the child's own intake of seafood contaminated with methylmercury, which has a much shorter elimination half-life than the highly persistent PCBs.

The serum was analyzed for specific antibodies against the two toxoids, diphtheria and tetanus. The results were as follows from the two examinations:

Antibody (IU/mL)	Number	Geometric mean	50% range	Total range
Diphtheria (1)	463	0.12	0.05-0.40	0.002-6.4
Diphtheria (2)	386	12.4	6.4-26	0.40-200
Tetanus (1)	463	0.22	0.09-0.51	0.004-120
Tetanus (2)	387	32.4	15-90	0.11-610

The antibody concentration increased by an average of 260-fold and 510-fold for diphtheria and tetanus, respectively. The highest ratios occurred in children examined about one month after the vaccination. However, due to substantial variability, the interval since the booster was not significantly associated with the post-booster antibody concentration or the ratio. Overall, the study design was successfully carried out, although some loss to follow-up happened, and the time of the second examination was not as well defined as had been intended.

The variability of post-booster antibody concentrations can probably in part be ascribed to small differences in the interval since the booster vaccination. In addition, children probably show different rates of response to the booster. This finding is somewhat surprising, because assessment one month after the vaccination is standard practice in vaccinology. However, assessment at this time would seem less suitable for identifying adverse effects of immunotoxicant exposures.

In regard to the pre-vaccination data, the diphtheria antibody concentrations decreased at increasing PCB exposure. A doubling of the serum PCB concentration was associated with a decrease in antibody concentration of about 25%. This finding is very similar to the results from the pilot study. Mercury also showed a negative association, though most likely due to confounding with PCB. Tetanus again showed a weaker effect.

The post-booster results showed a poor association with the children's exposure biomarkers. Even when the post-vaccination results were adjusted for the pre-vaccination results, no clear effects were seen. The statistical analyses are still ongoing.

In addition to comparing the antibody outcomes with PCB exposures assessed at different times, an opportunity also existed to examine the possible association with two integrated measures of PHAH exposures. One relied on the induction of estrogen-like properties, especially those mediated through interaction with the nuclear estrogen receptor. In addition, 2,3,7,8-tetrachlorinated dibenzo-p-dioxin (TCDD) and related substances interact with the intranuclear arylhydrocarbon receptor (AhR). Because a variety of substances may act as agonists or antagonists, assessment of complex exposures is complex, when effects are mediated via receptor interaction.

In this project, we used serum to assess the receptor activity in vitro, where activation was expressed by a reporter gene in a cell line. We used the E-screen and the lipid-adjusted aryl hydrocarbon receptor (AhR) activity as the two approaches to measure xenoestrogenic responses resulting from the combined exposure to the endocrine disrupting chemicals, and to assess the potential correlates of the xenoestrogenic activity, very little of which is known. The E-screen was conducted by stripping the serum for endogenous hormones and adding the extract to the MCF-7 breast cancer cell line, where induced growth was assessed in regard to the response induced by estradiol (E2).

The Ah receptor assay, serum or hexane-extracted serum lipophilics were added to cell line with a GFP reporter gene ligated to multiple copies of activated AhR-binding sites in the CYP1A1 promoter, and the activity was calibrated to that of TCDD. In both cases, we applied serum from the 34th week of pregnancy of the birth cohort mothers.

Increased E2 and AhR activities were found in some of the serum samples. Correlations were then assessed from lipid-based concentrations of individual organohalogens determined in the serum. The main finding was that β-HCH, p,p'DDE, and CB-118 were significantly negatively correlated with the E2 activity ($r=-0.22$, $p=0.004$; $r=-0.15$, $p=0.05$; $r=-0.16$, $p=0.03$ respectively). β-HCH and dieldrin were negatively correlated with AhR ($r=-0.26$, $p=0.002$; $r=-0.23$, $p=0.006$).

However, we failed to identify any single organohalogen substance responsible for the induced E2 and Ah activities, several negative associations were found. These findings are in accordance with the notion that the receptor activation is a result of complex interactions that are difficult to disentangle from measurements of individual agonists or antagonists. However, the results suggest that the E2 and Ah activity measure may be useful as integrated exposure indicators.

When used at statistical predictors for antibody concentrations at age 5 years, no clear pattern was revealed. However, these parameters will be included as exposure biomarkers in the structural equation models currently being developed.

All exposure biomarkers are associated with imprecision and risk of misclassification. The routine practice of comparing individual PCB congener concentrations with outcomes runs into the additional problem of multiple comparisons. We chose to avoid this problem by calculating to PCB exposure indices from the congeners most prevalent and therefore also most likely the ones determined with the greatest precision.

In further analyses of the cohort data, structural equation models will be used. Here the exposure variables will be assumed to reflect a latent, true exposure, which is not observed but can be modeled from the data. In these models, the observed PCB concentrations were considered manifestations of a latent true exposure, which, in turn, was assumed to affect each of the two antibody concentration outcomes. The latent exposure variable was assumed to depend on maternal blubber intake (dietary questionnaire response), and covariates were allowed to correlate with the latent exposure and the outcome. Unlike standard regression techniques, this approach takes into account measurement error in the exposure variables. In addition, a more powerful analysis is obtained, because information from different exposure markers is pooled.

We have used this approach in our pilot study, where we showed that it is highly feasible and powerful. The models will include sex, age, birth weight, and maternal smoking during pregnancy. Residual plots were used to assess the model fit, and regression results were also compared with the estimated dose-response functions from generalized additive models. An effort will be made to separate the relative effects of prenatal exposures (from maternal PCB concentrations) and postnatal exposures, as determined from the child's serum concentrations at age 18 months (N ~ 100, pilot study) and 5 years.

We calculated the benchmark dose as the PCB exposure that increased the risk of an abnormal response from the anticipated 5%–10%. To take the statistical uncertainty into account, the lower 95% confidence limit of the benchmark dose was then calculated, in accordance with previously established procedures.

Technical aspects

This study benefited from the advantageous epidemiological setting in the Faroe Islands. This population is exposed to elevated concentrations of PCBs from their traditional diet, which includes blubber from the pilot whale, a small toothed whale in which persistent contaminants are biomagnified. However, some Faroese eat very little traditional food, and a few eat a lot, so PCB concentrations range over two orders of magnitude, and the average exposure exceeds the US average by about 10-fold.

An additional advantage is that prospective cohort studies have been carried out in this population for over 20 years, and that the population is served by a single-provider government-owned health care system, which facilitates follow-up. Participation rates are generally close to 90%, although with lower rates for blood sampling from children.

The study protocol called for the first examination to occur just before the booster vaccination at 5 years of age. Only in one child had this vaccination already been done by the time of the first examination. For some children, the booster was delayed, whether due to incident disease, travels, or other reasons. However, the main problem in regard to the second clinical examination was that the children had already participated once, had recently been vaccinated, and therefore were more likely to refuse an additional blood test. Still, a participation rate above 70% is quite remarkable under these circumstances.

Childhood immunizations represent a standardized challenge to the children's immune system, a challenge that is not otherwise available or appropriate. This project focused on specific antibody reactions to protein toxoids, because they depend on the functions of several types of immune cells. The antibody assay has been standardized and is a routine analysis at national laboratories, such as the State Serum Institute in Copenhagen, Denmark.

Despite the fact that this population-based cohort of children was in good health, the antibody concentrations varied substantially. Known or suspected risk factors contributed very little to explaining this variability. In this connection, the significant effect of PCB exposure would therefore seem remarkable.

The Faroese population is exposed to PCBs at a much higher level than the US population, but the results suggest that possible adverse influences on the immune function may well occur also at lower exposure ranges prevalent worldwide. Further exploration of this issue will depend on the calculation of benchmark dose results.

Exposure assessment is always associated with a certain degree of imprecision. The use of biological samples for analysis of exposure biomarkers represents a substantial improvement, but these parameters are known to depend on a variety of factors, such as sampling time and the temporal characteristics of the exposure. These biomarkers may not necessarily reflect the exposure at target organ level at the time of the greatest vulnerability. Such imprecision will generally be non-directional and will cause a bias toward the null. In this protocol, the greatest possible effort was therefore made to control and minimize any error sources.

In regard to the PCB analysis, recoveries were >96% for the congeners measured. Within-day repeatability and between-day reproducibility showed a coefficient of variation < 8%. The quality control and accuracy is ensured by biannual participation in the external quality program (EQUAS) organized under the auspices of the German Society of Occupational Medicine and Environmental Medicine (Prof. Dr. H.Drexler, University Erlangen-Nuremberg, Erlangen, Germany). Likewise, mercury analyses are secured by participation in the Canadian external quality assurance program.

The antibody concentration assays were carried out using WHO-approved protocols, and the results were expressed in international units. The wide variability of the results is not affected by the slight analytical imprecision.

The two cell-based assays were comparatively labor-intensive. Given that neither of them showed a clear association with specific exposure parameters or outcomes, their use in future studies in this field needs to be considered with some skepticism.

Overall, this study provides supplementary epidemiological evidence for an association between exposure to environmental pollutants and a reduction of antibody production after routine childhood immunizations.

Implications

Among chemicals persistent in the environment, Polyhalogenated aromatic hydrocarbons (PHAHs), and polychlorinated biphenyls (PCBs) are listed as Priority Persistent Bioaccumulative Toxic Chemicals by the U.S. Environmental Protection Agency, and PCBs have been said to constitute the leading chemical risk from fish consumption. They are included in the Stockholm Convention. While average PCB exposure levels have decreased over the last 25 years or so, the number of fish advisories due to PCB contamination has steadily increased as knowledge on the extent of PCB pollution has expanded.

Immunotoxicity as an outcome of pollutant exposures is of considerable relevance to human health. Studies of children born preterm have shown that small differences in immune competence can result in changes in antibody production. Even if small differences may be of limited importance with regard to the protective effects of the vaccines as such, the functional deficits represent a quantitative measure of immune system functions that may relate to possible increases in the risk of infections in general. In addition, such alterations in immune function, when incurred during development of the immune system, are likely to be permanent and could therefore impact on an individual's future health and immune-related disease risk.

A further concern is that individual immunity must be reached in a certain proportion of the population to achieve 'herd immunity'. If this proportion falls below what is necessary for a particular disease, then the population as a whole loses its protected state, and an infectious epidemic may result.

This study was designed to assess whether prenatal and postnatal exposure to PCBs impacts on antibody response to childhood immunizations. The major advantages of this study were: detailed follow-up of an established and well characterized birth cohort of sufficient size examined at appropriate ages within the time period of a 3-year grant; occurrence of developmental PHAH exposure with a mixture of PCB congeners similar to the one prevalent in North America, an exposure range that spans a 100-fold interval, and an average in excess of the US level; application of sensitive and appropriate methods of documented feasibility with regard to assessment of exposures and outcomes; and a high statistical power due to the above characteristics that will allow advanced statistical analysis including structural equations and benchmark analyses.

This epidemiological study of healthy children provides evidence of pollutant-induced reduction of antibody production following routine childhood immunizations. Although subtle, such immune function impairment could become clinically important when the immune function is challenged by other factors such as preterm birth, chronic infection, or other disease. In addition, even slight impairments could be important at a population level, e.g., with regard to an increased prevalence of respiratory tract infections.

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Journal Article	Heilmann C, Grandjean P, Weihe P, Nielsen F, Budtz-Jørgensen E. Reduced antibody responses to vaccinations in children exposed to polychlorinated biphenyls. *PLoS Medicine* 2006;3(8):e311. Abstract Available Full-Text Available	R830758 (2005) R830758 (Final)	• Abstract from PubMed • Full-text: PLOS Journals Full Text EXIT Disclaimer • Other: PLOS Journals PDF EXIT Disclaimer

Supplemental Keywords:

cumulative effects; dioxin; dose-response; epidemiology; human health; hypersusceptibility; infants; marine food contamination; methylmercury; mixed exposure; prenatal exposure delayed response; risk assessment; sensitive populations,, HUMAN HEALTH, ENVIRONMENTAL MANAGEMENT, INTERNATIONAL COOPERATION, Scientific Discipline, RFA, Health, PHYSICAL ASPECTS, Risk Assessment, Risk Assessments, Health Risk Assessment, Physical Processes, Children's Health, Biochemistry, Environmental Policy, Exposure, exposure assessment, exposure model, health effects, developmental effects, developmental toxicity, immunotoxicology, children's environmental health, prenatal exposure, post-natal exposure, dietary exposure, pesticide exposure, pesticides, vulnerability, pregnant women, PCB, children's vulnerablity, Human Health Risk Assessment, polychlorinated biphenyl

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