



Quality of Life and Management of Living Resources

Key action 4.1

Disease and allergies related to or influenced by the environment, their prevention and treatment

QLK4-CT-2000-00279 Plutocracy

**Placental Uptake and Transfer of Environmental Chemicals
Relating to Allergy in Childhood Years**

Final report summary

Annexe I: Project Progress Summary

Project Summary: March 2001 – February 2006

Section 1: PROJECT IDENTIFICATION Information to be provided for project identification		NOT CONFIDENTIAL
Title of the project Placental Uptake and Transfer of Environmental Chemicals Relating to Allergy in Childhood Years		
Acronym of the project		PLUTOCRACY
Type of contract	Shared cost RTD project	Total project cost (in euro) 2,132,298 €
Contract number QLK4-CT-2000-00279	Duration (in months) 60 Months	EU contribution (in euro) 1,566,192 €
Commencement date 1 st March 2001	Period covered by the progress report (e.g. 1 February 2000 – 31 January 2001) 1 March 2001 – 28 February 2006	
<u>PROJECT COORDINATOR</u>		
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Key words (5 maximum - Please include specific keywords that best describe the project.). Allergy, Environment, Childhood, Pollutants, Pregnancy		
World wide web address (the project's www address) http://www.bris.ac.uk/plutocracy/		
List of participants Provide all partners' details including their legal status in the contract i.e., contractor, assistant contractor (to which contractor?).		
P1.	Coordinator	University of Bristol, Bristol, United Kingdom
P2.	Contractor	Slovak Medical University, Research Base of the SMU - Institute of Preventive and Clinical Medicine, Bratislava, Slovakia
P3.	Contractor	University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
P4.	Contractor	VITO, Vlaamse Instelling voor Technologisch Onderzoek NV, Mol, Belgium
P5.	Contractor	Emory University, Atlanta, United States of America
P6.	Contractor	University of Antwerp, Wilrijk, Belgium
AP2.1	Assistant Contractor to P2	Comenius University, Bratislava, Slovakia
AP3.1	Assistant Contractor to P3	National Research and Development Institute for Environmental Protection, Bucharest, Romania

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Section 2: Project Progress Report

NOT CONFIDENTIAL

(2 pages maximum.. Use short sentences. Be factual. Avoid technical terms as much as possible)

Objectives:

*To study the link between exposure of the unborn child to environmental pollutants during pregnancy and the later development of allergies in early childhood.

*To determine whether contamination of the placenta by environmental pollutants has an effect on placental function and the immune responses of the child at birth and during childhood.

*To investigate whether enhanced exposure to pollutants affects health outcome.

Results:

Recruitment of subjects. Pregnant women were recruited from 5 regions of varying environmental characteristics from within the EU: urban - Mol (Belgium); urban/industrial - Bratislava (Slovak Republic), Bucharest (Romania); agricultural - Giurgiu (Romania); rural - Stara Lubovna (Slovak Republic). A total of 788 pregnant women were recruited from maternity hospitals across the five regions before delivery according to specific inclusion criteria and informed consent was obtained. Following delivery, biological samples were collected which included maternal peripheral blood (PB), cord blood (CB) and placental tissue which were stored appropriately for further laboratory analysis. Mothers completed a questionnaire after delivery which covered information related to environmental exposure, health, lifestyle, medication, socio-economic factors, pregnancy and delivery. Samples of breast milk were collected from the mothers during the sixth week after delivery, where possible. Children underwent a clinical examination at the age of 18 months, including evaluation of allergic manifestation. A peripheral blood sample was collected from the children at this time and a postnatal questionnaire was completed by the mother. A wide range of laboratory analyses were performed on the collected samples which included chemical analysis of selected environmental xenobiotics (XB), total and specific IgE levels and cytokine profiles. The atopic status of the mothers within the cohort was assessed on the basis of maternal allergic history, sIgE levels in blood samples, or a combination of both according to a series of hierarchical definitions. Based upon the strictest case definition combining both allergic history and sIgE levels, % atopic ranged from the lowest value of 10% in Stara Lubovna and Bucharest to the highest value of 39% in Mol, highlighting significant differences between both regions and countries.

In utero environmental exposure. *In utero* environmental exposure was assessed from biological samples collected after delivery. Lead and cadmium were analysed in maternal blood and placental tissue and a large range of more than twenty organochlorine pollutants was analysed in maternal blood, placental tissue and breast milk samples. Significantly higher concentrations of lead and cadmium were found in the two Romanian regions compared with Belgium and Slovakia with the lowest lead concentrations found in Belgium and the lowest cadmium concentrations found in Slovakia. The highest organochlorine insecticide concentrations were found in Romanian biological samples and the lowest in Slovakia. Levels of chlorinated benzenes and PCBs were more comparable between the countries, being slightly lower in Romania and slightly higher in Belgium. The most predominant compound was p,p'-DDE in each of the biological matrices. Results suggest a wide variation in exposure to organochlorines across the regions, mainly with respect to pesticides. Concentrations of β -HCH, DDE and DDT were significantly higher in all Romanian biological samples compared with Belgium and Slovakia but there was no clear trend for PCB exposure.

Epidemiologic assessment of exposure. Questionnaires to obtain information about prenatal exposure, placental and newborn parameters were completed as part of the recruitment process. A total of 782 questionnaires were completed. The questionnaires were administered shortly after delivery in the maternity hospitals and the data entered into Epi-Info data screens, prior to analysis. Antenatal predictors were analysed with respect to elevated cord blood IgE levels, and higher maternal education level, residence in a house, residence in a city, residence near heavy traffic and exposure to agricultural chemicals all showed a positive association.

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Modulation of placental function and fetal sensitisation. Recent studies have suggested that elevated cord blood (CB) IgE may be an early marker of allergic disease in children so we investigated whether there was an association between maternal allergic disease status, antenatal exposures and CB IgE. The highest levels of CB IgE positivity (> 0.35 kU/l) were found amongst Romanian neonates and the lowest amongst Slovakian neonates. Mothers of CB IgE positive neonates were more likely to have a higher education level, reside in the city, reside in a house, near heavy traffic, near agricultural fields and to be having the walls painted or the home redecorated during pregnancy. Animal ownership and smoking patterns were also found to differ significantly between CB IgE positive and negative outcomes. In contrast, the allergic disease status of immediate family members, with the exception of siblings of neonates, did not differ according to CB IgE outcome. The placental concentrations of DDT, DDE, γ -HCH, α -HCH and 1,3,5-TCB were significantly increased in mothers with neonates positive for CB IgE levels. The relationship between placental contamination and indicators of placental and immune function was investigated using samples from participating subjects in each region. Exposure to toxic metals and organochlorine insecticides was shown to influence immune function in placental tissue, maternal and cord blood as shown by alteration in cytokine production profiles and IgE levels. However, there was no clear evidence of polarisation of the response perhaps due to restricted sample numbers.

Kinetics of placental transfer and fetal biodistribution. Placental transfer experiments performed using laboratory models clearly demonstrated the ability of selected organochlorine compounds (DDE, DDT, DCB, PCB-77/PCB-52) to transfer across the placenta from the maternal to the fetal circulation (and vice versa). Transfer was demonstrated to occur by passive diffusion in the human perfused placenta model with significant accumulation within the perfused area observed for DDE, DDT and PCB-77 but not DCB which transferred across most rapidly. In an animal model, fetal organ uptake reached a peak within 24 hours of maternal exposure, clearly demonstrating *in vivo* placental transfer. Preferential uptake occurred in certain fetal organs including liver, spleen and bone-marrow for certain organochlorines which may have implications for immune function or development in the exposed fetus and requires further study.

PM_{2.5} and PM₁₀ exposure. Group exposure data for PM_{2.5} and PM₁₀ concentration continued to be collected in Slovakia and initial analysis shows differences between the two regions being studied, with the levels higher in Bratislava. Group level exposure data from Romania and from monitoring stations in Belgium were evaluated alongside the Slovakian data. At this stage, there appears to be no correlation with outcome due to the overlap of ranges of values for both PM_{2.5} and PM₁₀ between the regions. Further analytical approaches are being considered.

Postnatal exposure and risk assessment. Sensitisation in children at 18 months of age as assessed by sIgE to specific allergens ranged from 0% in Bucharest to 6% in Giurgiu and was lower than expected compared with other studies, perhaps due either to age or geographic location (majority in Eastern Europe). There were no significant regional differences but this may be due to low numbers of positive subjects. In contrast to allergic sensitisation, the highest incidence of allergic symptoms in offspring was found in Belgium which correlates with maternal atopy prevalence. There were significant regional differences and predictors for atopic eczema included allergy to cow's milk or other foods, recent ill health such as 'flu or recent fever, cough, runny nose and daycare outside the home. Th1 and Th2 CK production by cord blood cells was elevated in children in Belgium and Slovakia with atopic eczema by 18 months of age but only Th2 CK production was elevated in peripheral blood cells which may suggest a postnatal bias. Asthma symptoms do not generally appear until later in childhood so later follow-up of the cohort is important.

Overall, this study provides valuable data on gestational exposure to persistent pollutants in different area of Europe which will inform future biomonitoring and health intervention studies.

Benefits and Beneficiaries:

Preliminary statistical analysis has been completed but further detailed analysis is being undertaken

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and results will be disseminated to the appropriate audiences and the benefits will become evident as the results are translated into policy. Results will be publicised through academic peer-reviewed publications, seminars, provision of information to appropriate government health bodies, International networks/organisations and dissemination on the Internet. This will improve information on the health status of European citizens including health status and relation between environment and health.

Publicity of the results from this project will be used to promote a healthier lifestyle with the provision of advice for expectant mothers on reduction of their exposure to pollutants. This study will provide information to aid the reduction of people's exposure by informing the public of the key risks and mitigate the effects on exposed individuals by providing more information on the precise relationship between *in utero* exposure to pollutants and the long-term health of the citizen.

Future Actions (if applicable): Publication in peer-reviewed literature and further dissemination