

**EUROPEAN NETWORK ON CHILDREN'S SUSCEPTIBILITY AND EXPOSURE
TO ENVIRONMENTAL GENOTOXICANTS QLK4-CT-2002-02198**

CHILDRENGENONETWORK

SUMMARY REPORT

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Abstract

The Concerted Action, Children Genotoxicity Network, explored gene-environment interactions during the foetal, neonatal and infancy developmental periods, concentrating on genotoxic exposures and environmental factors with focus on air pollution (traffic and tobacco). Six relevant research areas (work packages) were chosen and covered by 16 European research groups. The work packages are: 1) Literature study of (cyto)genetic data on children and protocol for establishment of a pooled database, 2) Mother Child cohorts/survey, 3) Placental exposure, 4) Impact of air pollution on pregnancy outcome and child development, 5) Risk assessment, 6) Ethics.

Since the kick-off meeting in February 2003, work has progressed and is now finalised.

Work package 1 has evaluated several studies analysing the effects of children's exposure to chemical environmental pollutants with biomarkers of genetic damage. A number of biomarkers resulted to be consistently increased in children (MN, CA, DNA and protein adducts). MN show increasing frequencies with age even in children.

Work package 2 identified several mother/child cohorts within Europe with biobanks enabling follow up studies with biomonitoring and developed a webpage, accessible to the community. (<http://www.birthcohorts.net>)

Transplacental transport is investigated in work package 3.

A pilot family study has been performed in work package 4 with samples from 24 families (12 mothers with 2 children in a polluted and 12 in a less polluted area). The family study was designed from studies in Czech Republic which showed the impact of air pollution on pregnancy outcome identifying critical windows of exposure.

Pilot studies have been initiated in Belgium, The Netherlands, Hungary, UK, Norway, Spain and Greece to explore adult vs. child/newborn gene expression, DNA repair and susceptibility. A pilot study has been completed in Norway to explore cord blood RNA sample collection in large biobanks. Also work-package 3 has initiated pilot studies of placental transfer in Denmark and Finland. All pilot studies were supported by additional national funding

In work package 6 (Ethics) state of the art in studies with focus on ethical issues in pre- and post-natal studies on children have been summarized. Special ethical issues arise from studies of environmental health contrary to clinical studies and clinical trials. These issues are related to incentives to participate, data protection, data storage and dissemination. Discussions of maturity age and assent/consent from children are also important.

The network is described at website <http://cgn.pubhealth.ku.dk>.

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1. Objectives

CHILDRENGENONETWORK is a European network providing input and data for risk assessment at the national and European level. This Concerted Action explored gene-environment interactions during the foetal, neonatal and infancy developmental periods, concentrating on genotoxic exposures and environmental factors with focus on air pollution (traffic and tobacco).

The Concerted Action of the CHILDRENGENONETWORK aimed at collecting, validating and reviewing the available, though few, European and other studies and study materials on children's exposure and susceptibility to genotoxicants, with focus on air pollution. A further aim was to prepare protocols to conduct feasibility studies with perfused placenta and with mothers and their children (two siblings), where research would be financed by national or other sources. Environmental exposure to genotoxic compounds, either during foetal life or during childhood, may induce damage to children's health, and thereby increase risks of childhood cancers and other diseases. The network would form the basis for future projects within Europe, including new partners and with weight on exchange and mobility of young researchers.

Six relevant research areas (work packages) have been chosen to cover all aspects of these areas. 16 research groups with appropriate expertise have been in close collaboration.

2. Summary of the ChildrenGenoNetwork – results of each work package

WP 1 Literature study of (cyto)genetic data on children and protocol for establishment of a pooled database

In this work package published and unpublished studies on children groups screened for cytogenetic biomarkers, DNA and protein adducts, *HPRT* and *GPA* mutation frequency, DNA fragmentation (Comet assay) were searched, with particular attention to studies where also genetic metabolic polymorphisms were measured. European pooled cohorts were created for meta-analysis and re-analysis purposes. Examples of exposures are combustion products from traffic, heating and industry, radiation and pesticides.

The major findings were that:

MN: age related increases, significantly lower frequencies in newborns;

CA, MN, but not SCE (confirmed in meta-analysis): consistently increased in children exposed to environmental chemical pollutants;

DNA, albumin and haemoglobin adducts: consistently increased in children exposed to airborne urban pollutants;

haemoglobin adducts: increased after passive exposure to tobacco smoke (meta-analysis)

hprt, GPA mutation frequency; Comet assay, FISH: too limited evidence.

WP1 received very good evaluation at the midterm review and the reviewers encouraged the network to optimise the exploitation and dissemination of all the data collected from cytogenetic studies with children.

The lessons from this work package suggest elaboration of protocols for future studies with children with emphasis on sufficient power of the studies (number of study persons), exposure characterization and quality control of data.

- Available data on cytogenetic endpoints (MN, CA, and SCE) related to environmental exposures and radiation have been successfully statistically analysed
- Existing data on other biomarkers (e.g., adducts) were not accessible for meta-analyses
- New upcoming biomarkers need to be validated in studies in comparison with traditional biomarkers
- Additional information may be obtained from existing material/cohorts regarding

genotypes, DNA repair, and antioxidative status

- Sensitivity of tests in children should be specifically evaluated with respect to e.g., numbers of cells counted

WP 2 Mother-child cohorts/survey

An overview of the existing European cohorts which includes biological material and describing exposure information collected in these cohorts was made. An interactive website presenting all European mother/child cohorts (www.birthcohorts.net) has been set up. This website has already obtained much attention. It has proved that it is possible to establish a user-friendly web-site, which allows frequent updating and expansion. Feasibility studies on RNA isolating in the Norwegian MoBa cohort have been performed. The webpage is aimed to serve as a tool for facilitation of comparative and collaborative studies of early life exposures and child health. The webpage obtains much attention from many stakeholders and will be maintained and further developed, hopefully within the frame of other EU-projects. It has proved possible to establish a user-friendly web-site which allows frequent updating and expansion. Collaborative studies are requested cohort-based prospectively designed studies related to environmental health, since studies of interaction between exposure and genes require large sample sizes and furthermore since the outcome of interest – fortunately – most often is rare.

- Collaborative studies are requested within this area
- Large sample sizes are needed in cohort-based prospectively designed studies related to environmental health
- Triad studies (including fathers) are recommended
- Standardized protocols for biosampling, processing and storage are requested

WP 3 Placental exposure

In utero exposure and genetic events are studied by the placental perfusion system with the ultimate aim of establishing the biologically effective dose of genotoxins from environmental tobacco smoke and ambient air pollution. Important results are expected from the testing of transplacental transport of particles and benzo[a]pyrene and other test substances. The work package has contributed to the development of protocols for placental perfusion studies to be implemented in integrated projects of NEWGENERIS (Newborns and Genotoxic exposure risks) and ReProTect .

Since the placental perfusion system only works in a few European laboratories (Oulu, Bristol, Copenhagen and Kuopio), collaboration gave a good opportunity to train a young scientist in the methodology. Important results are seen from the testing of transplacental transport of particles and benzo[a]pyrene and other test substances.

WP 4 Impact of air pollution on pregnancy outcome and child development

The existing literature on the impact of air pollution on pregnancy outcome and child development was reviewed as the starting point for a number of feasibility studies, which employed specific genotype assays and microarrays-based gene expression assays to delineate potential variations in the efficiency of DNA husbandry and susceptibility to genotoxins in children and adults. Cytogenetic damage (MN and FISH) was measured in 24 Czech families (mothers and two siblings) in Prague and Copenhagen. Differential gene expression analyses of the children were performed at the University of Maastricht. Furthermore WP 4 (and WP 1 and WP 5) has initiated several feasibility studies with national funding:

- A pilot study of DNA repair in mothers versus newborn child - Brussels
- Telomeric length as a biomarker of individual susceptibility in children - Barcelona
- Pilot analysis of bulky DNA adducts in younger children - Hungary
- The effect of lead exposure on MN in children in Silesia province – Poland
- The impact of environmental exposure of Polish children to complex mixtures (heavy metals and PAHs) on DNA damage and repair including the effect of gene polymorphism
- Comparison of DNA sensitivity, repair efficiency, apoptosis and necrosis between lymphocytes from child and adult populations exposed to external agents as well as DNA damage-repair, apoptosis, and necrosis in child, adult and old age humans – Greece

- Results from a pilot study, evaluating RNA blood collection tubes (PAXgene Quiagen) and Tempus (ABI) used for cord blood in large biobanks, and exploring factors of importance in the maternity units; in collaboration with the Norwegian biobank MoBa - Norway
- DNA damage in mothers and babies - UK
- Tight planning of collaborative studies with protocols available in English and agreements on handling and storage of samples are recommended
- The pilot study of the Czech children demonstrates the usefulness of the combined measures of cytogenetic damage and transcriptomics in environmental health biomonitoring
- The network facilitated national funding
- National feasibility studies may contribute to EU biomonitoring pilot study in 2006

WP 5 Risk assessment

The main goal is the identification of critical health effects suitable for quantitative risk assessment in children in different developmental periods (foetal period, neonatal period, early childhood) and the use of biomarkers of exposure, of early effects and of susceptibility in the process of risk assessment. The second goal is the adaptation of available risk assessment approaches for the assessment of health risks posed by genotoxic air-pollutants during the foetal period and in early childhood.

The work package was successfully launched in 2003 with a workshop and finished in 2005 by the concluding workshop 27-30 October in Italy.

Available information has been supplemented with national studies of existing and newly established study populations with children. Much has been extracted from existing studies and more is available. New studies should be designed from optimal protocols taking sample size into account to ensure sufficient power of the study.

WP 6 Ethics

This work package summarizes state of the art in studies with children and focus on ethical issues in studies on placental tissue, studies during pregnancy and on children ensuring that ethical considerations are integrated in all the stages of the project. Informed consent for feasibility studies has been included. Implications of (and possible conflicts between) the rules laid down in the Council of Europe's Bioethics convention and its associated protocols, the EU GCP directive, the recently revised WMA Declaration of Helsinki, and national regulations concerning research ethics have been taken into account.

The states of the art in studies with focus on ethical issues in pre- and post-natal studies on children have been summarized. The work package successfully initiated the debate on specific issues in relation to research with children in the workshop in Copenhagen December 2003, as published on the CGN website. To further discuss the special ethical issues related to environmental health/public health a follow up meeting took place in Krakow 2005 15-18th May. The outcome will be points to consider in future environmental health research with children.

- Special ethical issues arise from studies of environmental health contrary to clinical studies and clinical trials. These issues are related to incentives to participate, information, data protection, data storage and dissemination. Discussions of maturity age and assent/consent from children are also important.
- Ethical issues, social and legal impacts of studies with children need more exploration as geographical and cultural differences were found.

3. Conclusions and statements

The CGN demonstrated availability and usefulness of existing data relating biomarkers to children's environmental exposure.

The network also initiated a number of national studies which contribute excellent platforms for intervention and adherence to the upcoming pilot project on human biomonitoring in Europe.

The pilot project demonstrated usefulness of one of the new omic techniques, namely transcriptomics to which relevant expectations as new monitoring tool is stated.

All such new techniques need validation and comparisons to traditional biomarkers are recommended.

Mother-child cohorts or more relevant triad studies including the fathers are useful constructions for sampling and biobanking with the aim of surveillance of the exposure of the general population and specific research projects.

Risk assessment related to children's exposure to environmental toxicants must take age specificity into account and more data about exposures and effects are needed for proper assessment of differential susceptibility.

Ethical issues and social and legal impacts of studies with children needs more exploration as geographical and cultural differences are seen.

Statements

- Novel and promising biomarkers of effect have become available, which upon proper validation need to be applied, in addition to classical biomarkers within foreseen European biomonitoring/surveillance programs.
- Thereby also focusing on children's environmental health risks as highlighted by the SCALE initiative. Birth cohorts have been shown to represent rich resources of data that are either already available or will be when established.
- Such cohorts are worthwhile to be mined for gene environment interactions concerning multiple child diseases, provided that state-of-the-art technology is used when sampling biomaterial such as blood.
- Follow-up studies of the birth cohorts later in life should be foreseen
- Cytogenetic data obtained till now indicate that children are not necessarily more susceptible to environmental genotoxins compared with adults.
- Future research should therefore focus on the question raised by the SCALE initiative whether the one child is more susceptible than the other
- Multiple polymorphisms interaction should be studied
- Ethical issues in relation to biomonitoring studies of children and environmental health need further ethical consideration which takes the child's interest into account.
- Informed consent, data protection and biobanking deserved special attention

These statements were developed at the CHILDRENGENONETWORK concluding workshop in November 2005.

4. Tables summarizing the deliverables of the work packages

Work-package No	Work package title	Responsible Participant No	Person-months in budget	Person months in cost statements	Participants	Deliverable(s) No ³⁹
WP 1	Literature study of (cyto) genetic data on children and protocol for establishment of a pooled database.	14	28	40	1,3,6,7,13,14,15	D2-D6
WP 2	Mother child cohorts/survey	1	12	12	1,3,4,5,7,8,14,15	D7-D9
WP 3	Placental Exposure	2	12	12	1,2,10,11	D10-D14
WP 4	Impact of air pollution on pregnancy outcome and child development	3	15	25	1,3,4,5,6,7,8,9,12,,14,15,16	D15-D21
WP 5	Risk Assessment	3	1	1	all	D22-D28
WP 6	Ethics	1	12	15	all	D29-D33
WP 7	Project Management	1	9	9	all	D0-D1 D34-D45

Deliverable No	DELIVERABLE TITLE	Delivery Date
D0	Glossy leaflet brochure about the CA	4 Printed in 3000 exemplars and distributed at several occasions
D1	Web site about the project	2 Established www.cgn/pubhealth.ku.dk; many visits
D2	Database with studies identified by nationality, study group, exposures, data of studies, outcome, references.	12 Protocol issued data base established and used for metanalysis
D3	Publications with major findings.(3-5)	34 5 publications
D4	A protocol for meta-analysis of data	34 Developed
D5	Review paper (s) on available studies with DNA adducts and DNA-Single Strand Breaks (SSB) with European children, analysing relationship between biomarkers and exposure.	34 Newborns covered in D15
D6	Review paper(s) on available studies in children, analysing the effect of metabolic genotype polymorphisms on endpoints.	34 To be published by Sram <i>et al</i> later
D7	An overview of available child/mother cohorts	24 Meetings 23rd /24th of May 2004 and 6th of June 2005 and development of website which has been presented by Anne Marie Nybo Andersen at workshops in Bangkok and US.
D8	A study plan for larger collaborative cohort studies with questionnaires	34 Part of D7 and promoted by the www.birthcohorts.net developed with support from CGN
D9	A symposium or workshop suggestion at the 31 st Conference of European Teratology Society. Sep 6-10.2003 in Denmark	10 Symposium successfully held the 7th September. Poster of the network was also presented at the EEMSs meetings in Aberdeen 2004 and Kos 2005
D10	Feasibility of placental perfusion as a model for foetal exposure to environmental genotoxins	34 Protocols in Oulu, Kuopio, Copenhagen to be published
D11	Feasibility of new markers (in blood) of DNA interactions by these compounds (DNA dosimetry)	34 Performed in Sweden (PAH) and UK (particles)
D12	Study protocol for mother/cord blood study.	34 Ongoing in Finland, Belgium and DK as part of nationally funded studies
D13	Protocol for comparable measurements of DNA repair capacity, geno-types and DNA damages after in vitro challenging in blood from umbilical cord/mother	34 Ongoing in Belgium and UK as part of nationally funded studies
D14	A symposium or workshop suggestion on reproductive toxicity for the International Congress of Toxicology (ICT-X) to be held in Tampere Finland in July 2004	2 11th of July 2004 a meeting on placental perfusion was held
D15	Report of the impact of air pollution on pregnancy outcome and child development.	12 Review by Radim Sram <i>et al</i>
D16	Report of the feasibility of conducting a study on gene expression among children exposed to air pollution coming from traffic exhausts and environmental tobacco smoke.	34 Status meeting held in Prague 20th-22nd of January 2005 2 publications from Czech pilot study submitted
D17	Study protocol for exposure monitoring and blood sampling and processing	34 Available in Czech

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D18	Identification of potential genetic biomarkers for risk assessment	12 Reported in D3
D19	Detailed protocol for such a study regarding gene expression.	34 Reported in D16
D20	Report on pilot DNA expression study	34 Reported in D16
D21	Report on the pilot study	34 Reported in D16
D22	A workshop with the aim to resume the state of the art regarding risk assessment and children.	4 Held in Prague March 2003 and followed up at meeting October 2005
D23	Proceedings from workshop	12 Reported in D16
D24	Review of exposure assessment in children	36 D3 and D16
D25	Review of DNA repair in children compared with adults	24 Reported in Belgium study also supported with national funding
D26	Review of risk assessment approaches with the aim of estimating risk in children	12 To be developed from the conclusions of the CGN in relation to NEWGENERIS
D27	Conference on the assessment of health risks posed by genotoxic exposure in foetal and early childhood periods	32 PINCHE, PLUTOCracy and CGN meeting in Brussels November 2005
D28	Conference proceedings: Summary of suitable risk assessment approaches	Summary of network activities as presented in Kos 2005 and Brussels 2005 with posters and abstracts displayed at website
D29	Informed consent forms for studies within this concerted action network.	12 Report by Raymond Ubaghs
D30	European meeting on ethical aspects in studies on placental tissue and during pregnancy and childhood.	2 Held the 5-7th of December 2003 and Krakow June 2005
D31	Published proceedings of the meetings on ethics.	24 3 publications under preparation
D32	Survey of European informed consent procedures regarding placental tissue and newborns	24 D29
D33	Survey of European informed consent procedures regarding children	24 D29 and Report by Raymond Ubaghs
D34	Quality assurance plan	0 Distribution of workplan to each partner
D35	Partnership agreement	0 Done
D36	Kick off meeting report	4 Done
D37	Midterm review	24 Prior to EEMS meeting Maastricht 3.9.2004
D38	Annual reports	34 Delivered 2003 and 2004
D39	Annual cost statements	34 Delivered 2003 and 2004
D40	Progress report (mid-term)	18 Done
D41	Cost statement (mid-term)	18 Done
D42	Final project report	38
D43	Final cost statement	38
D44	Proposals for workshops at European conferences	2 EEMS-meetings in Maastricht 2004 and Kos 2005, PINCHE-meetings in London 2003 and Bruxelles 2005 Bradford meeting 2005
D45	Proposals for young scientists to exchange between partners and the application of supplementary funding	2 Several visits performed; exchange of students by visits of Danish students to Kuopio and UK post doc to Poland, Polish Master student to Bradford and Danish master student to Brussels and Maastricht.

5. List of publications

Articles published in scientific journals

- Gabriella Bognár, Gabriella Mészáros, Katalin Szalma, Péter Brunner, Katalin Lelkes, György Köteles (2005): Cytogenetic base values in children. *Egészségtudomány (Health Sci)* 49: 40-45 (in Hungarian)
- Jerzy Brusilo, Ethics of genetics research on children: Christian philosophy and Catholic theology in Niebrój L., Kosińska M., (eds.), *Health care: professionalism and responsibility*, Katowice: Wyd. ŚAM, 2006 -in press
- Kogevinas M, Nybo Andersen A-M, Olsen J. Collaboration is needed to co-ordinate European birth cohort studies. *Int. J. Epidemiol.* 33 (2004) 1172-3
- György Köteles (2005): Radiation protection: protection of children. *Egészségtudomány (Health Sci)* 49: 30-39 (in Hungarian) (a review paper)
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- Monica Neri, Alexandra Fucic, Lisbeth E. Knudsen, Cecilia Lando, Franco Merlo, and Stefano Bonassi. Micronuclei frequency in children exposed to environmental mutagens: a review. *Mutat. Res.* 544 (2003):243-254
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- L. Niebrój, Health education and children: the parental guardianship [in Polish], *Ann Univ Mariae Curie Sklodowska [Med]* 2004, 59 (Suppl. 14/4): 199-203
- Doina C. Obreja, Gabriella Mészáros, Rodica Tulbure, Gabriella Bognár, Eugen S. Gurzau, György Köteles (2005): Lymphocyte micronucleus frequencies in children living in lead-polluted environment. *Centr. Eur. J. Occup. Environ. Med.* 11: 21-26
- Radim Sram, Blanka Binkova, Jan Dejmek, and Martin Bobak: Ambient air pollution and pregnancy outcomes. *Environ Health Perspect.* 113(2005)375-82
- Natalie P. Wyatt, Lucyna Kapka, Adolf Baumgartner, Ewa Siwinska, Danuta Mielzynska, Lisbeth E Knudsen and Diana Anderson. Lead exposure in mothers and children from an industrial region of Poland: an assessment of micronuclei using fluorescence in situ hybridisation. Does lead contribute to increased micronuclei levels? *Journal of Preventive Medicine* (accepted)
- Natalie Wyatt, Christine Kelly, Vincenzo Fontana, Domenico Franco Merlo, Donald Whitelaw and Diana Anderson. Effects of the heterocyclic amine 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx) on human lymphocyte DNA in diabetic and non-diabetic population sub-groups: an assessment using the Comet Assay Susceptibility in human lymphocytes to MeIQx, *Journal of Preventive Medicine*, 13 (2005) 17-23
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- Danuta Mielzynska, Ewa Siwinska, Lucyna Kapka, Krzysztof Szyfter, Lisbeth E. Knudsen, Domenico Franco Merlo. Environmental exposure to complex mixtures including PAHs and lead and genotoxic effects in children living upper Silesia, Poland (submitted).
- Marie Pedersen, Peter Vinzents, Joergen Holm Petersen, Jos Kleinjans, Micheline Kirsch-Volders, Gina Plas, Miroslav Dostál, Pavel Rössner, Olena Beskid Radim J. Šrám, Domenico Franco Merlo, Lisbeth E. Knudsen Cytogenetic effects in Children and Mothers exposed to Air Pollution assessed by the frequency of micronuclei and fluorescence in situ hybridization (FISH). A Family Pilot Study in the Czech Republic (submitted).
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- Muszynska-Graca M., Mielzynska D.: Mother's exposure and disease as a health risk factor to her child – review of mother-child cohort studies in Poland (in preparation).
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- Kirsi Vähäkangas, Franco Merlo, Lisbeth E. Knudsen: Biobanking of samples from environmental health studies with children (in preparations).
- Kirsi Vähäkangas, Paivi Myllynen ,Vyvyan Howard: Placental transport of particles (in preparations).
- Kirsi Vähäkangas, Paivi Myllynen , Dan Segerbäck: Placental exposures and PAH (in preparations).

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- <http://www.pubhealth.ku.dk/CGN>
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- Merlo D. F., Knudsen E. L., Vähäkangas Kirsi. Ethical issues related to children

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- Pedersen M., Knudsen L. E. Ethical issues related to individualised biomonitoring studies of children
- Pedersen M., Vinzents P., Petersen J. H., Kleinjans J., Kirsch-Volders M., Plas G., Dostál M., Rössner P, Šrám R. J., Knudsen L. E.. Micronuclei in families exposed to air pollution. A pilot study in the Czech Republic
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6. Activities within the ChildrenGenoNetwork from 2003 to 2005

The CHILDRENGENONETWORK (CGN) was initiated by the 1st January 2003 and has progressed within all workpackages as described below.

All partners have been active participating in meetings and providing inputs for deliverables as stated in the technical annex.

A kick-off meeting assembled all partners the 2-3rd February (Professor Piperakis unfortunately had a car accident on his way to the airport and had to send his apologies). Minutes are available on the website.

The network management group met as scheduled at the **NordEMS meeting in Bornholm June 15-18** (Kirsi Vähäkangas and Franco Merlo sent their apologies, Ian Cotgreave was invited to detail the planning of WP4) and **in connection with the workshop concentrating on ethical issues in Copenhagen December 2003** (Micheline Kirsch-Volders sent her apologies).

The workshop on risk assessment arranged by Radim Sram in Prague 16-19th March had been planned before the official initiation of the CGN by the EU Center of excellence, Academy of Sciences of the Czech Republic and the CGN in collaboration. 35 attendants were present (15?) of whom were covered by the CGN. The rest were local and US-speakers financed by the Center of excellence.

A symposium '**Prenatal Influences on Health in later life**' was arranged and supported by the CGN in connection with the **ETS meeting 7-10th September in Elsinore**. Anne Marie Nybo Andersen was chairing the session and Joern Olsen gave the introductory speech. 'Pre- and perinatal causes of disease with a late onset – the background of the national birth cohort'.

A site visit took place in Vilnius 16-19th October with the aim of establishing contacts with Professor Lazutka and his collaborators for collecting Lithuanian data on children. Participants were Franco Merlo, Stefano Bonassi, Lisbeth Knudsen, Lazutka and dr. Slapsyte and Dr. Naginiene from Institute for Biomedical Research of Kaunas University of Medicine, Kaunas, The **20-23rd October a site visit in Oulu** was arranged by professor Kirsi Vähäkangas and dr. Paivi K Myllynen to demonstrate the placental perfusion system to Lisbeth and co workers (Galina Plesner and Louise Grave Larsen). This was followed by another site visit by Lisbeth, Louise and Galina in Aarhus to visit Olav Pedersen, working with an alternative set up of the perfusion system

On the 1st November another site visit was taking place in Stockholm to develop the protocol of WP4. Participants were Radim Sram, Jos Kleinjans, Ian Cotgreave, Edyta Barak, Steffen Loft and Lisbeth Knudsen.

On the 27th November Lisbeth, Inger-Lise and Micheline were kindly invited by professor Koteles for a site visit at the **National research institute for radiobiology and radiohygiene, Budapest**

On the 4-7th December the conference Ethical aspects in studies on placental tissue and during pregnancy and childhood was held in Copenhagen with 44 participants. Presentations are available on the website.

On the 13-14th January Steffen Loft gave a presentation at the nanoparticles meeting in Liverpool, acknowledged to the CHILDRENGENONETWORK

On the 20th-22nd February Lisbeth Knudsen, Franco Merlo, Diana Andersson and Adi Baumgartner site visited the Institute of Occupational Medicine and Environmental Health in **Sosnowiec, Poland** to collect further information about Polish data and exchange protocols in ongoing national studies initiated by the concerted action.

In weeks 9-11 sampling took place in Czech Republic with presence of Peter Vinzents, Marie Pedersen (airs ampling) and Edyta Bajac (blood processing).

The 19-21st March Dan Segerbäck and Lisbeth Knudsen visited **Maastricht** to prepare the midterm review meeting with Jos Kleinjans.

The 31st March-2nd April Lisbeth Knudsen gave a presentation of the network at the **PINCHE** meeting in **London**. Stelios Piperakis also gave a presentation, acknowledged to the network. Other participants at this meeting were Anne Marie Nybo Andersen, Diana Anderson, Natalie Wyatt, Louise Grave Larsen and Galina Plesner.

The 13-15th April a planning meeting for the pre-workshop to the International Congress in Toxicology (ICTX) was held in **Kuopio** by Kirsi Vähäkangas with attendance of Dan Segerbäck, Lisbeth Knudsen and Päivi Myllunen.

The 22-24th May a Workshop on Birth Cohorts in Europe was held in **Copenhagen** with more than 20 participants. **Anne Marie Nybo Andersen** was hosting on behalf of WP2.

June 16-20th Anne Marie Nybo Andersen visited professor Manolis Kogevinas in **Barcelona** for the preparation of an inventory of European mother/child cohorts with samples.

July 11th WP 3 Preconference meeting on PLACENTAL STUDIES Workshop on various aspects of fetal exposure to chemicals – on-going studies and future perspectives was held at Hotel Victoria **Tampere** with 20 participants.

Lucyna Kapka from Institute of Occupational Medicine and Environmental Health in **Sosnowiec, Poland** was a visiting scientist at the **University of Bradford** 5th July-4th September. She analysed MN in peripheral lymphocytes of 82 children by FISH with pan-centromere probe. Dr. **Bernadette Schoket** (2005) replaced Prof. Dr. György Köteles (2003-2004), in the scientific management of the CGN-related Hungarian activities in 2005 after his retirement as director of his affiliation. Administrative management of the CGN activities has been under supervision of Dr. G. Köteles.

September 3-4th 2004 the midterm review took place prior to the European Environmental Mutagen Society (EEMS) annual meeting, in Maastricht. Jos Kleinjans, University of Maastricht hosted the meeting. The status and the results of the network were presented at the annual EEMS meeting in Maastricht and the 2004, annual meeting of the Belgian Society for Toxicology and Ecotoxicology by Lisbeth E. Knudsen. M. Pederson from the Institute of Public Health Copenhagen (Prof. E. Knudsen) spent two weeks at the VUB laboratory (Prof. M. Kirch-Volders) to learn the MN technology and got **training in MN scoring**. She applied this expertise for the biomonitoring of children exposed to air pollution in the Czech Republic. **October 24-27th 2004** the first biennial Central and Eastern European Environmental Health Conference took place in Prague, Czech Republic, organised by Radim Sram and with Alexandra Fucic attending. A follow-up **seminar on WP4 Impact of air pollution on pregnancy outcome and child development**, organised by Radim Sram, was held in Prague **January 20 - 22nd 2005**. A webpage presenting all European mother/child cohorts (<http://www.birthcohorts.net>) was launched at the **workshop on European mother/child cohorts**, organized by the DG Research and CGN in Brussels 7th June 2005. To further discuss the special ethical issues related to environmental health/public health a follow up meeting to the ethical workshop in Copenhagen was held June 16-18 2005 a **meeting on ethics of genetic research: children, families and society** in Krakow. Franco Merlo participated in PhD course on ethical issues in epidemiology Finland June 20-22, organised by Kirsi Vähäkangas. The Network was represented at **the annual meeting of the European environmental mutagen society** at Kos in July 1-7th .2005. Diana Anderson organized an international meeting on **Male mediated Developmental Toxicity** followed by the **annual UKEMS** meeting in Bradford, August 1-5th 2005. Gunnar, Radim and Lisbeth participated and gave oral presentations. In October **the concluding seminar of CHILDRENGENONETWORK, with focus on risk assessment and children** was organised by Franco Merlo. Together with PINCHE CGN has organized a **conference on results from EU framework 5** in November 2005.

Activities related to the ChildrenGenoNetwork

During 2003, environmental health and children has become a priority issue in the EU as stated in the **Aarhus meeting: An Environment for better health, May 8-10 and in the SCALE initiative**. Scientific evidence, focused on Children, meant to raise Awareness, improve the situation by use of Legal instruments and ensure a continual Evaluation of the progress made (<http://brussels-conference.org/project.htm>). Thus the coordinator was invited to Aarhus, attended the stakeholder meeting in July, where SCALE was launched and has been appointed co chair in the TWG Biomonitoring of children as well as to be a **member of the TWG for research needs**. A. Fucic was appointed as a member of the TWG Biomonitoring. The coordinator has attended several meetings within these TWGs and provided input for the reports. An invited presentation on biomonitoring of children, including results from the CHILDRENGENONETWORK was given in **Dublin, Ireland** the 30th April 2004. Danuta Mielzynska, Ewa Siwinska and Danuta Kapka organized **Satellite workshop: Cytogenetic Markers in Assessment of Human Exposure to Carcinogenic Substances in the framework of Gliwice Scientific Meetings 2003**, November 21-22, 2003. In May 2004 Danuta Mielzynska and Ewa Siwinska were invited to participate in **Bridges in Life Sciences Workshop focused on reproductive health and perinatal problem of low birth weight** in Bratislava. The coordinator and Franco Merlo were invited to meetings in US/ILSI in September 2004. **Lisbeth, Alexandra, Radim and Diana** participated at International Conference within The European Environmental & Health Action Plan 2004-2010 in Egmond aan Zee, December 2004 presenting activities of CHILDRENGENONETWORK. **Lisbeth, Kirsi and Radim were invited to participate in the IPCS workshop on toxicogenomics and the risk assessment** of chemicals for the protection of human health, organised by WHO December 2004 in Berlin. Lisbeth was invited to participate in a **meeting organised by the DG research** 10th October 2005 in Brussels regarding 'Environmental issues related to food and feed'. DG research hosted a **workshop** "Synthesising research results for supporting human biomonitoring in Europe"- Brussels, 21 November 2005 with participation of Jos Kleinjans and Lisbeth.

Information, dissemination

Information about the CGN-project has been disseminated by the glossy leaflet brochure which was printed in 3000 copies and has been distributed at many meetings etc attended by the participants in the network. The website of the project has been well visited and the website is periodically updated.

To strengthen the collaboration with the PINCHE and the PLUTOCRACY project the coordinator participated in the meeting for the PINCHE groups of Air pollution and Carcinogenicity in Stresa, September the 21st and the CGN was also presented at the PINCHE meeting in London 31st-2nd April 2004: 3rd International Conference on children's health and the environment: putting children into science and policy.

The coordinator participated in national activities regarding Environment and Health and Children initiated by the Danish research centre for Environment and Health Research Fund (one day conference the 12th May) and the Danish Board of Technology (consensus paper on children and the environment). A **seminar on children's health and the environment in Denmark** April the 4th 2006 is under preparation under supervision of Lisbeth.

National and international fundraising related to CGN

The coordinator has raised funds for two national projects related to the CGN: 'Follow-up studies of children participating in asthma study with the aim of investigating the importance of genetic polymorphisms within metabolism of air pollutants' (530,000 DKK) and Transplacental transport of environmental toxicants (596,000 DKK).

Professor Kirsi Vähäkangas has raised money to set up the perfusion system in Kuopio, Finland.

Professor Micheline Kirsch Volders has initiated study of sensitivity of mother/daughters to exposures.

Professor György Koteles has initiated laboratory measurements to get background cytogenetic data on children. The Hungarian partner greatly appreciated the invitation to join the CGN. Participation in the project helped to obtain better information on the international activities in the newly emerging research field of environmental genotoxic exposure of children, become part of the international streamlines, and initiated efforts to start new and strengthen traditional local activities. We regretted that lack of national research funds greatly hindered us to make a strong and substantial contribution to the network activities. All the same, the partnership in the network was undoubtedly an important driving force to obtain small national research funds during the network period. Eventually, we were able to contribute with new data of our cytogenetic pilot studies; we investigated key methodological aspects of using aromatic DNA adducts as biomarkers of low-level environmental genotoxic exposure; and added our local experience on some ethical issues of conducting environmental epidemiological study among children.

Professor Diana Anderson has provided £2,000 for preparation of reference material and initiated a study: investigating the effect of different chemicals on mother/child cohorts of diabetic and non-diabetic individuals to assess differences in susceptibilities between diabetic populations of different ethnic origin and lifestyle habits using the Comet assay.

Professor Gunnar Brunborg has initiated a project at the Norwegian Institute of Public Health, receiving support from FUGE (Functional Genomics – a research programme supported by the Norwegian Research Council), for the study of blood sample RNA quality and its suitability for gene expression analysis. The blood samples were collected within the Mother & Child project, which comprises 100,000 births with cord blood samples as well as blood samples from the mother and father. Initial experiments study the sampling, transportation and storing conditions of cord blood /adult blood optimal for

preserving RNA. Conditions in the maternity units of importance for satisfactory sampling have been identified. Results and procedures used are communicated with Partner No 9. Ian Cotgreave now has a full time position at the AstraZeneca with associations to Karolinska providing opportunities of testing with highly updated methods of toxicogenomics.

Dan Segerbäck submitted an application to the Swedish Research Council for funding a more extensive collaboration with Kirsi Vähäkangas on the placental system (application was not granted). However, an application with the same content was funded by the Swedish Animal Welfare Agency (300,000 SEK). A student Kirsi Annola from Kirsi Vähäkangas grupp received a Nordforsk grant in 2005 to stay in Dan Sagerbäcks lab (will take place second half of 2006). Marie Pedersen from University of Copenhagen received a exchange fellowship in 2005 to follow-up on the MN and microarray analyses in Maastricht University

Danuta Mielzynska and her team has raised about 40,000 Euro from the Polish State Committee for Scientific Research for a project : “DNA damage in children environmentally exposed to lead with the assessment of individual susceptibility for toxic effect of lead, and genetic polymorphism of lead biotransformation and mechanism of DNA repair” – for 2003 – 2006.

Aleksandra Fucic participated in the launching of the national collaborative project in R Croatia “Biomedical research of reproduction and development (coordinator Prof D. Jezek, Medical faculty, Zagreb) which raised 20,000 Euros.