Juha Pekkanen • Matti Jantunen • Raimo Pohjanvirta
Raimo O. Salonen • Jouni T. Tuomisto • Matti Viluksela
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Centre for Environmental Health Risk Analysis 2002–2007

Final Report for the Finnish Programme for Centres of Excellence in Research

Kansanterveyslaitoksen julkaisuja B 20/2008

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CENTRE FOR ENVIRONMENTAL HEALTH RISK ANALYSIS 2002-2007

Final report for the Finnish Programme for Centres of Excellence in Research

Kansanterveyslaitos
Ympäristöterveyden osasto

KTL-National Public Health Institute, Finland
Department of Environmental Health

Helsinki 2008

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ABSTRACT

General objective of the *Centre for Environmental Health Risk Analysis* was to improve environmental health risk analysis by increasing the understanding of environmental risks at all levels from molecular mechanisms to societal needs. This required both high-quality research and better methods of risk characterization.

For both dioxin and urban air particulate pollution (PM), the present risk assessment practices do not optimally benefit human health. Fish may contain toxicants, but its nutrients are beneficial for health. Risk assessors and authorities have recommended restrictions to fish consumption, even if the net effect on health is negative. We calculated that by reducing salmon consumption in Europe, one might cause 100-fold more loss than saving of life. Current urban exposures to PM are calculated to cause 350 000 premature deaths annually in Europe while cancers due to urban air metals (As, Cd, Ni) are by far fewer and more uncertain. Still the carcinogenic metals are strictly regulated on the basis of occupational data and experimental animal data, but there is little legislative effort to effectively reduce current PM exposures.

Effective risk assessment requires a thorough knowledge of the full causal chain leading to health effects. Own scientific research is needed to be able to interpret and to fill in the gaps in the available information. The Centre's work focused on developing innovative methods for assessment of exposure and for doing risk analysis, on understanding the mechanisms of adverse effects through toxicological, molecular biology, and human studies, and on multidisciplinary collaboration between exposure scientists, toxicologists, epidemiologists, and risk analysts both in field works and in risk analysis. Internationally important and relevant scientific results were achieved for both dioxin and PM.

In all of these areas international and domestic collaboration with high-standard scientific institutes has been crucial, and we have been able to establish permanent networks that will be highly important also after this project has ended.

Keywords: Air pollution, fine particles, ultrafine particles, coarse particles, exposure, epidemiology, toxicology, dioxins, TCDD, developmental toxicity, teeth, risk analysis, risk assessment, open risk assessment

Juha Pekkanen, Matti Jantunen, Raimo Pohjanvirta, Raimo O. Salonen, Jouni T. Tuomisto, Matti Viluksela, Jouko Tuomisto
Ympäristöterveyden riskianalyysin huippuyksikkö 2002-2007. Loppuraportti Suomen kansalliseen tutkimuksen huippuyksikköohjelmaan
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TIIVISTELMÄ

Ympäristöterveyden Riskianalyysin Huippuyksikön perustavoite oli parantaa ympäristöterveyden riskianalyysiä parantamalla ymmärrystä terveysriskeistä kaikilla tasoilla molekyyleistä yhteiskunnan tarpeisiin. Tämä tavoite edellytti sekä korkeatasoista tutkimusta että tutkimusmenetelmien parantamista riskin luonnehdintaan.

Sekä dioksiinien että kaupunki-ilman pienhiukkasten osalta nykyinen riskinarviointi ei edistä parhaalla tavalla ihmisen terveyttä. Kalassa on epäpuhtauksia, mutta sen ravintoaineet edistävät terveyttä. Riskinarvioijat ja viranomaiset ovat suositelleet tiukkoja rajoituksia kalan käyttöön, vaikka rajoitusten nettohyöty on negatiivinen. Arvioimme, että vähentämällä lohen kulutusta Euroopassa estetään ehkä joitakin syöpiä, mutta vastineeksi saadaan satakertainen määrä sydänkuolemia. Kaupunki-ilman pienhiukkasten on arvioitu aiheuttavan 350 000 ennenaikaista kuolemaa vuodessa Euroopassa. Ulkoilman metallien aiheuttama syöpäriski on paljon pienempi ja epävarma. Siitä huolimatta metalleja säädellään tiukasti työterveystutkimusten ja eläinkokeiden perusteella, kun taas pienhiukkaspitoisuuksiin on puututtu haluttomasti.

Hyvä riskinarviointi edellyttää terveyshaittaan johtavan syy-seuraus ketjun kaikkien vaiheiden tarkkaa tuntemista. Tieteellisen kirjallisuuden ohella olemme tarvinneet omaa tutkimusta pystyäksemme tulkitsemaan muiden tuloksia ja täyttääksemme tiedon aukkoja. Huippuyksikkö keskittyi kehittämään parempia menetelmiä arvioida altistusta ja tehdä riskianalyysia ja haittojen mekanismien ymmärtämiseen hyödyntäen toksikologista, molekyylibiologista ja epidemiologista tutkimusta. Toimintaa leimasi monitieteisyys altistustutkijoiden, epidemiologien, toksikologien, and riskianalyytikkojen välillä sekä kenttätöissä että riskianalyyseissa. Sekä dioksiinien että pienhiukkasten osalta on saatu kansainvälisiä huipputuloksia.

Kansainväliset yhteydet ja yhteistyö ovat olleet ratkaisevia tutkimukselle ja ne ovat auttaneet luomaan verkostoja, joiden hyöty ulottuu kauas hankkeen päättymisen jälkeen.

Avainsanat: ilmansaasteet, pienhiukkaset, altistus, epidemiologia, toksikologia, dioksiinit, TCDD, kehityshäiriöt, hampaat, riskianalyysi, riskinarviointi, avoin riskinarviointi

Contents

1 EXECUTIVE SUMMARY

Risk assessment is used in a variety of areas of life. This has led to different traditions which are not necessarily in line with each other. In risk assessment of chemicals, it seems that epidemiological approach leads to different level of regulation than toxicological approach. It also seems that cancer risk is treated differently from the risk of cardiorespiratory death. From the societal point of view, it is important that resources are allocated in such a way that they produce real added value. Therefore, the general aim of the Centre for Environmental Health Risk Analysis has been to "increase the understanding of environmental risks at all levels from the biochemical and molecular mechanisms to the society".

The starting point of this Centre was to compare the risk assessment of dioxins, chemicals typically regulated on the basis of toxicological data in animals, and fine particulate matter ($PM_{2.5}$), complex mixture air pollutants typically regulated on the basis of epidemiological data on human populations. The available data on both dioxins and fine PM were planned to be screened from the level of basic biological mechanisms of action to the level of society, screen for similarities and differences between the two, and propose new paradigms, if the present risk assessment would lead to erroneous results or put an emphasis to such a direction that the society is not best served.

It became clear during the exercise that, both in dioxin regulation and in $PM_{2.5}$ regulation, the present risk assessment practices do not optimally benefit human health. The risk assessment of chemicals takes place in isolation, and indirect consequences are not taken into account. A prime example is fish consumption. Fish contains a number of chemical contaminants, dioxins, polychlorinated biphenyls, organochlorine pesticides, and methyl mercury. On the other hand, fish oils are beneficial for health, and fish is an important source of several minerals and micronutrients. These other aspects are assumed to be taken care of in the risk management step, but in practice this does not happen. Hence, risk assessors and authorities are prone to recommend severe restrictions to fish consumption, even if the net effect of restrictions on health is clearly negative. We calculated that by reducing farmed salmon consumption in Europe, one would prevent 0–50 cancer cases per year, but increase cardiac deaths in the order of 5000 per year. An example among air pollutants is a skewed decision of European Commission on limit or target values of $PM_{2.5}$ as compared to some carcinogenic metals (As, Cd, Ni). Current exposures to $PM_{2.5}$ are calculated to cause 350 000 premature

deaths annually in Europe. Only a small percentage of these are due to cancer, and there are little data to assign this to the specified carcinogens. However, the carcinogenic metals are strictly regulated on the basis of occupational human data and experimental animal data, but there is little legislative effort to effectively reduce current $PM_{2.5}$ exposures.

Development of effective risk assessment methods requires a thorough knowledge of all steps of the development of injury. Part of this information can be retrieved from international scientific literature, but to be able to do that, and also to be able to fill in the gaps in data when necessary, our own scientific research was necessary in several relevant areas. We performed thorough mechanistic research to understand the mechanisms of dioxins and PM in causing their adverse effects in susceptible population groups and the society.

We contributed effectively to understanding the effects of dioxins on developmental effects and cancer. Especially, the effects on tooth development were illuminating. This endpoint seems to be one of the most sensitive effects of dioxins in rats, and the range of concentrations needed was not far from the present concentrations in general population. Comparing these effects to human findings after a dioxin accident in Seveso, Italy, and slight mineralization abnormalities in Finnish children made it possible to delineate the safe levels of dioxins more accurately than before.

One of the difficulties in dioxin risk assessment has been the huge variation among species and even strains of the same species. We were able to find rules of this variation by combining toxicological, genetic and molecular biology research, usually in collaboration with national and international groups. Developmental effects seemed to be quite consistent over different genetic backgrounds, and this gives much improved basis for risk assessment. On the other hand, carcinogenicity appeared to be variable even among strains of rats, but on the other hand it may be a secondary high-dose phenomenon less important than developmental effects from the risk assessment perspective.

Exposure analysis has been an integral part of this Centre. In environmental health research, exposure is often the weakest point of analysis, and may lead to highly erroneous conclusions and decisions. We had available a first-class accredited analytical laboratory for dioxins, and have now a good knowledge of Finnish exposure to dioxins, polychlorinated biphenyls, and polybrominated diphenylethers. Also the sources have been analysed by other groups in the Institute, and we have created a thorough understanding on the potential health effects of these chemicals in Finland and internationally. This has also given us authority to influence decisions especially in the European Union and World Health Organisation, and indirectly even in the U.S.

When this Centre started, practically nothing was known on the mechanisms of cardiac effects of fine PM. Panel studies among ischemic heart disease patients illuminated both the sources of $PM_{2.5}$ exposure and also the direct effects on clinical parameters and inflammatory markers, and are still ongoing. An association was shown for the first time between ultrafine and fine particles with risk of myocardial ischemia as indicated by electrocardiogram changes. Among the cardiac patients and adult asthmatics, the negative effects of $PM_{2.5}$ were most strongly associated with particles originating from local combustion.

Our collaborative epidemiological studies have clearly shown an association between air pollution and cardiovascular hospitalizations, but also fatal stroke. This could be demonstrated even in the Northern parts of Europe, although the levels of particles are only one fifth of those in the South. Apart from respiratory effects in the elderly, particles were also associated with children's asthma visits in hospitals.

By collecting air particles using a high volume cascade impactor, it became possible to collect large enough amounts of particulate mass in different size ranges for a series of mechanistic studies. In parallel cell and animal studies, it was possible to compare the inflammatory, cytotoxic and genotoxic activities of ultrafine, fine and coarse particles from various source environments with different chemical characteristics. This gave possibilities for delineating the physicocemical characteristics crucial for the health effects. The results supported the epidemiological findings of the Centre that local sources of incomplete combustion and resuspended road dust have a key role in urban PM-related health effects. Extension of the new methods on PM sampling, and chemical and toxicological characterisation to specific emission sources like small-scale wood burning installations and vehicle engines using biofuels will facilitate contributions to decision-making and development of new emission reduction technologies.

Also in the assessment of health impact of PM, exposure analysis has been an integral part of our work. New methodologies were developed and distributed internationally especially within EC projects. A general trend was to understand exposure and exposure variation also at individual level, not only at population level. One of the problematic questions in PM is to find out reliably the sources of various components, and hence the possible differences in the health impacts of different emissions. Much effort was given to source apportionment analysis in several European cities. High on-road concentrations of traffic-related pollutants seemed to contribute significantly to the exposure to black carbon and several transition metals. A special feature in the risk studies of PM is the wildfires in Eastern Europe in 2002 and 2006. They were calculated having caused some additional mortality even in Finland.

Risk analysis was an integral part of all the projects, but additionally it focussed on developing methodology of doing risk assessment. One of the specific aims was to help developing integrated, holistic risk assessment methods, such that various risks could be compared and also benefit-risk assessment would be possible. This necessitated methods for quantitative modelling which utilised Bayesian methods, value of information, and expert elicitation approaches. One of the keys in these comparisons was giving up the built-in safety margins that prevent knowing at the end, what is the most likely risk. The risk assessor should give the best scientific estimate of the risk, with its uncertainty margins, to the risk manager. Some practical case studies were done to illuminate these methods, among them a benefit-risk assessment of farmed salmon, impact of replacing diesel busses with natural gas driven busses, and modelling "composite traffic" idea for Helsinki region, meaning demand-responsive minibus services as an alternative to private cars.

A special feature has been to develop the idea of Open risk assessment, which means a completely new method for making risk assessments. The major ideas are a) completely open participation in the assessment process; b) a systematic information structure based on a coherent ontology and causal connections between measurable objects; c) inclusion of value judgements within the assessment. In practice, the application of the Open risk assessment requires a wide electronic forum for performing assessments and collecting ideas and opinions from the public. The forum has been tested already for a year and a half, and the results are promising (see http://heande.pyrkilo.fi). The method for Open risk assessment and the related practical tools will hopefully aid in framing socially acceptable and comprehensive treatment for major risk assessment procedures.

The Centre has been highly international in its activities. The Centre coordinated 4 and was a partner in 15 major European projects. The collaborative network of the Centre has covered not only all main dioxin and PM research centres in Europe, but also several of those on other continents, e.g. the Harvard Center for Risk Analysis, MS, USA; University of Toronto, Canada; University of Wisconsin, Madison, USA; University of Okayama, Japan; and University of Western Australia.

Graduate and postgraduate training have been an integral part of the Centre. The Centre has produced 15 doctoral theses. All teams have collaborated closely in the Graduate School of Environmental Health, lead in 2002-2003 by prof. Jouko Tuomisto, in 2004-2005 by prof. Jukka Juutilainen, and 2006-2009 by prof. Juha Pekkanen. The main emphasis in the training of the School is on environmental health risk assessment, so the School's aims parallell closely those of the Centre.

2 PERSONNEL

2.1 Executive board of the center

Jouko Tuomisto (director 2002-2004), Juha Pekkanen (director 2004-2007), Matti Jantunen, Raimo Pohjanvirta, Raimo O. Salonen, Jouni T. Tuomisto, Matti Viluksela.

2.2 List of other researchers

Aarnio, Päivi
Ahokas, Anne
Alm, Sari
Asikainen, Arja
Hakulinen, Pasi
Halonen (Kettunen), Jaana
Hannila, Marja-Leena
Happo, Mikko
Hujo, Mika
Hälinen, Arja
Hänninen, Otto
Ilacqua, Vito
Jalava, Pasi
Jetsu, Aleksi
Koistinen, Kimmo
Korkalainen, Merja
Lanki, Timo
Leino, Olli
Lensu, Sanna
Linden, Jere
Miettinen, Hanna
Mäki-Paakkanen, Jorma
Niittynen, Marjo
Pennanen, Arto
Penttinen, Pasi
Rotko, Tuulia
Rusanen, Maria
Salmela, Satu
Scotto Di Marco, Greta
Sillanpää, Markus
Simanainen, Ulla
Tainio, Marko
Tarkiainen, Tuula
Tiittanen, Pekka
Timonen, Kirsi
Turunen, Anu
Vallius, Marko
Verkasalo, Pia
Viluksela, Matti
Wendelin, Dominique
Yli-Tuomi, Tarja

2.3 Significant expert tasks

Airnet: A Thematic Network on Air Pollution and Health (2002-2004). Memberships in all working groups: Exposure assessment (Matti Jantunen), Epidemiology (Juha Pekkanen), Toxicology (Raimo O. Salonen), Health Impact Assessment (Jouni T. Tuomisto), and Science-Policy Interface (Jouni T. Tuomisto).

EU SCALE Program: Technical Working Group Integrated monitoring of dioxins and PCBs in the Baltic Region (2003-2004), Basic report (148 pp), Recommendation for Actions (105 pp), chairman; Jouko Tuomisto.

European Food Safety Agency, Scientific Advisory Forum, Alternate member Jouko Tuomisto, participated e.g. in Dioxin Colloquium 28.-19.6.2004. organised by EFSA to coordinate opinions on dioxin risk assessment in different countries (incl. U.S.A. and Japan) and Colloquium on Risk assessment of compounds that are both genotoxic and carcinogenic 16.-18.11.2005.

International Society of Indoor air Quality and Climate, vice president 2000-2003; Matti Jantunen.

International Society for Exposure Analysis, past president, member of executive board; Matti Jantunen.

ISEA-2003 Conference, co-chair, Stresa, Italy, 2003; Matti Jantunen.

WHO Regional Office for Europe. Working group on Health aspects of air pollution with particulate matter, ozone and nitrogen dioxide. 13-15 January 2003, Bonn, Germany. Report EUR/03/ (94 pages). Temporary advisers; Juha Pekkanen and Raimo O. Salonen.

National Advisory Committee of the Ministry of the Environment for the EC-DG Environment ‘Clean Air for Europe’ (CAFE) Programme (2002-2004). Member; Raimo O. Salonen.

EC/JRC/IHCP (Ispra): CEM-TF Task Force on Consumer Exposure Model evaluation and harmonization (2003-04). Member; Matti Jantunen.

EC/JRC/IHCP (Ispra): Stratex Task Force to develop a research activity strategy for Unit for Physical and Chemical Exposure (2002-04). Member; Matti Jantunen.

WHO/IPCS, Geneva: Exposure Modelling Subgroup / Exposure Activity Planning Group. Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals (1999-2004). Co-chair; Matti Jantunen.

Joint WHO/ECEH – JRC/ECA Workshop and Report: Role of Human Exposure Assessment in Air Quality Management (2002-04). Chair; Matti Jantunen.

WHO/ECEH Expert group on Health Impacts of Transport Related Air Pollution, Bonn. Its document, WHO Monograph on Health Impacts of Transport Related Air Pollution was selected among the highest prioritised WHO documents for 2004. Chair; Matti Jantunen.

10th International Congress of Toxicology (ICT X, 2004), Scientific Program Committee (2002-2004) Member; Matti Viluksela.

EC/JRC/IHCP/ECVAM (Ispra): Scientific Advisory Committee of the European Centre for the Validation of Alternative Methods (ESAC) (2002-2004). Member; Matti Viluksela.

Nordic aspects of air pollution and health in Europe (NORDAIR). Concerted action of the Nordic Council of Ministers (2004-2005). Co-ordinator; Raimo O. Salonen.

European Science Foundation, COST Action 633 on Particulate matter: properties related to health effects (2002-2008). Steering committee and Management committee member & Health aspects working group chair; Raimo O. Salonen.

The Ministry of the Environment, National Advisory Committee for Air Pollution Abatement 2005-. Permanent health advisor; Raimo O. Salonen.

YTV Helsinki Metropolitan Area Council. Principal health advisor in air pollution abatement; Raimo O. Salonen.

FINE Particles - Technology, Environment and Health Technology Programme 2002-2005, Finnish Funding Agency for Technology and Innovation (Tekes). Rapporteur of health aspects in final programme reporting; Raimo O. Salonen.

Abatement strategies for air pollution and health effects from locally emitted and transnationally transported biomass combustion aerosols (NORDAIR-BIOS). Concerted action of the Nordic Council of Ministers (2005-2006). Co-ordinator; Raimo O. Salonen.

EC/DG SANCO (Brussels): Scientific Committee on Health and Environmental Risks (SCHER). Member; Matti Viluksela.

EC-FP7 Theme 6. Environment (including climate change) 2007-2013. Adviser in planning the subactivity 6.2 Environment and Health in 2005; Raimo O. Salonen.

WHO/Air Quality Guidelines, Global Update: Member of the Working Group; Matti Jantunen.

CEFIC Long Range Initiative: External Scientific Advisory Board member; Matti Jantunen.

U.S.EPA: Particulate Matter Star Grants Review Panel. Member; Matti Jantunen.

ISEE-ISEA Joint Conference September 2006 in Paris, France. Co-chairman; Matti Jantunen.

WHO: Development of Indoor Air Quality Guidelines.(2006-), Chairman of the Working Group; Matti Jantunen.

Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (FORMAS), Grant Review Panel on Environmental Toxicology. Member; Matti Viluksela.

National representative, EU Public Health Programme, Monitoring, Committee on Environmental Health; Juha Pekkanen.

Member, European Respiratory Society, Environmental Health Committee; Juha Pekkanen.

National Centre of Expertise Programme 2007-2013, Cluster of Environmental Technology. Chair of Executive Board of the Steering Committee of 'Climate, Air Quality and Health' -Technology Network; Raimo O. Salonen.

Safety and Security Technology Programme 2007-2013, Finnish Funding Agency for Technology and Innovation (Tekes). Member of Steering Committee on National Safety; Raimo O. Salonen.

North-Savo Thematic Programme on Energy and Environmental Technology 2008-2013, The Regional Council of Pohjois-Savo / EU Regional Development Fund. Scientific advicer; Raimo O. Salonen.

Finnish Particulate Forum (joint platform of industry, research funders and institutes, and administration). Annual Award 2007; Raimo O. Salonen.

2.4 Editorial and other tasks in international scientific journals

Pharmacological Reviews, Associate Editor; Jouko Tuomisto.

Pharmacology & Toxicology, Member of the Editorial Board; Jouko Tuomisto.

Toxicology Letters, Member of the Editorial Board; Jouko Tuomisto.

Environmental Toxicology and Pharmacology, Member of the Editorial Board; Jouko Tuomisto.

Scandinavian Journal of Work Environment & Health, Guest Editor of a thematic supplement issue 'Multidisciplinary research on urban air particles in Finland'; Raimo O. Salonen.

BMC Public Health, Member of the Editorial Board; Juha Pekkanen.

Indoor Air (Journal for Indoor Air Quality and Climate), Member of the Editorial Board; Matti Jantunen.

Journal for Exposure Analysis and Environmental Epidemiology, Associate Editor Matti Jantunen.

3 MOBILITY OF RESEARCHERS

Monique Franc, PhD, from Department of Pharmacology, University of Toronto, Toronto, Canada, visited KTL for 3 weeks in 2002.

Juha Pekkanen spent a year (2002-2003) at Instituto municipal de investigación médica (IMIM), Environmental and Respiratory Research Unit, Barcelona, Spain.

Yuri Bruinen de Bruin, PhD, from Joint Research Centre/University of Milan worked at KTL in 2002 for 3 months.

Norio Sogawa, PhD, from Department of Dental Pharmacology, Okayama University, Okayama, Japan, spent a year in KTL in 2002-2003 as a visiting scientist.

Kimmo Koistinen, PhD, from KTL is serving Post Doc term as visiting scientist at EC/JRC/Institute for Health and Consumer Protection in Ispra, Italy.

Benedict Jacquemin, MD, PhD student, from Centre de Recerca en Epidemiologia Ambiental -IMIM, Barcelona visited KTL in 2004 (3 months).

Markus Sillanpää, MSc, PhD-student, spent 2 months at the Process- and Aerosol Measurement Technology Division, University of Duisburg, Germany in 2003.

Benedicte Jacquemin, MD, from Centre de Recerca en Epidemiologia Ambiental - IMIM, Spain, worked as a visiting scientist at KTL for 4 months in 2006.

Vito Ilacqua, PhD, from Rutgers University EOHSI, New Jersey, worked as post-doc at KTL in 2002-2005 (total 28 months).

Marko Vallius, PhD, from KTL worked as Post Doc at the Telethon Institute for Child Health Research (12 months) and the University of Western Australia (3 months), in Perth, Australia, from November 2005.

Ulla Simanainen, PhD, from KTL is serving Post Doc term at the ANZAC Research Institute, Andrology Laboratory, the University of Sydney, from 2005.

Eva Kunseler, MSc, working as European projects manager at KTL, YTOS from 2006.

Timo Lanki, PhD, from KTL worked as Post Doc at Institute of Epidemiology, GSF, Germany in 2007 (13 months).

Miranda Loh, PhD, from Harvard worked as Post Doc at KTL from January 2007.

Markus Sillanpää, PhD, spent 10 months at the Department of Civil and Environmental Engineering, University of Southern California (USC), Los Angeles, USA in 2007.

4 PRODUCTIVITY, PROGRESS AND RESULTS

4.1 Total publications in 2002-2007

- 157 articles in refereed international scientific journals
- 30 articles in refereed international edited volumes and conference proceedings
- 4 articles in refereed Finnish scientific journals
- 14 scientific monographs (dissertations) published in Finland
- 1 scientific monograph (dissertation) published abroad
- 87 other scientific publications.

Full list of publications in Chapter 11.

4.2 Degrees earned within this project in 2002-2007

- 15 PhD or equivalent
- 4 MSc or equivalent.

4.3 Other products

Composite_traffic_1_0_1.ana. A model for computing vehicle traffic flows in Helsinki in different private car and composite traffic scenarios. In addition, the model calculates the costs of trips for passengers and society. Published as an additional file in BMC Public Health 2005: 5:123.

ExpoFacts: Open access website and database for European exposure factor data. http://cem.jrc.it/expofacts/

Open access websites for developing Open Risk Assessments (ORA). http://heande.pyrkilo.fi (in English), http://tyjak.pyrkilo.fi (in Finnish). The first ORA about Hämeenkyrö municipal solid waste incinerator published as an example.

4.4 Major teaching and dissemination achievements

4.4.1 Textbooks, special issues

Salonen RO (ed). Multidisciplinary research on urban air particles in Finland. Scand J Work Environ Health 2004; 30 suppl 2: 1-98. Thematic supplement issue of 10 internationally peer-reviewed articles + 3 introductory articles (CtrEx researchers as authors in 9 articles).

Hallikainen A., Penttilä P.-L., Penttilä U., Pohjanvirta R., Strandman T., Rajakangas L., Hänninen R., Blomberg K., Niemi E., Nuotio K. and Siivinen K. Riskiraportti – Elintarvikkeiden ja talousveden kemialliset vaarat. Elintarvikeviraston Valvontaopas-sarja 2/2002.

Tuomisto J. Ympäristölääketiede ja ympäristöterveydenhuolto (Environmental medicine and environmental health). In: K. Koskenvuo (ed.) Sairauksien ehkäisy (Textbook of Preventive Medicine), Duodecim 2003, 863-880.

Duodecim 2004;120:1643-1700, Special issue on Environmental Health (in Finnish), Guest editor: Jouko Tuomisto.

Tuomisto J. 100 kysymystä ympäristöstä ja terveydestä; arsenikista öljyyn. [100 questions about environment and health; from arsenic to oil.]328 p. Kustannus Oy Duodecim 2005

Koulu M, Tuomisto J (ed.). Farmakologia ja toksikologia [Pharmacology and Toxicology textbook], 1199 p. Medicina Oy 2007.

Mussalo-Rauhamaa H, Paile W, Tuomisto J, Vuorinen HS (ed.). Ympäristöterveys [Environmental Health textbook], 272 p. Kustannus Oy Duodecim 2007.

Jantunen M, Komulainen H, Nevalainen A, Tuomisto J, Venäläinen R, Viluksela M. Selvitys elinympäristön kemikaaliriskeistä - Kansallisen kemikaaliohjelman taustaselvitys [Evaluation on health risks of chemicals in our environment – Report for National Chemical Programme]. Kansanterveyslaitoksen julkaisuja B11/2005, 257p. http://www.ktl.fi/attachments/suomi/julkaisut/julkaisusarja_b/2005b11.pdf

Erkkola M, Fogelholm M, Huuskonen MS, Komulainen H, Korhonen M, Leino T, Nevalainen A, Paile W, Pekkanen J, Sala E, Salonen RO, Suni J, Taskinen S, Tuomisto J, Vartiainen T, Viluksela M. Children's environment and health. National CEHAP evaluation [In Finnish with English executive summary]. Publications of the National Public Health Institute, 2007, KTL B11/2007, 185 p.

Elintarvikehygienia – ympäristöhygienia, elintarvike- ja ympäristötoksikologia [Food hygiene – environmental hygiene, food and environmental toxicology] (toim. Hannu Korkeala) 497 p. WSOY 2007.

4.4.2 Major seminars

Deichmann Award Lecture (Plenary Lecture in the beginning of the X International Congress of Toxicology in Tampere 11.7.2004), Jouko Tuomisto on dioxin risk assessment.

Eurotox Merit Award Lecture (43th Congress of European Societies of Toxicology, Dubrovnik, 20.09.2006), Jouko Tuomisto on role of toxicology and risk assessment.

“Between Scylla and Charybdis”, EFSA-symposium in Helsinki 30.11.2006, Jouko Tuomisto on risk-benefit assessment in food regulation.

Session on Environmental Health at Tieteen päivät, Helsinki 11.01.2003.

An open international Workshop (50 participants) on the PAMCHAR project results 20 October 2004 in connection to the 3rd Annual AIRNET Conference in Prague, CZ. Organiser: Raimo O. Salonen.

EU DG-Research Open Stakeholder Consultation on the thematic area of Environment and Health for the 7th Framework Programme (22 May 2006, Brussels, Belgium). Stakeholder statement 'Importance of source-specific characterization of urban air particulate exposures and health effects for future policies' on behalf of the COST Action 633 on Particulate matter: properties related to health effects (Raimo O. Salonen).

EU DG-Research Workshop on Environment and Health ‘Towards a full chain framework of air quality and health through European research’, 12-13 October 2005, Brussels, Belgium. Three presentations on the 4th and 5th Framework Programme EU projects co-ordinated by the Centre of Excellence team leaders in 1996-2004: EXPOLIS (Matti Jantunen), ULTRA (Juha Pekkanen) and PAMCHAR (Raimo O. Salonen).

NORDAIR-BIOS Workshop ‘Abatement strategies for air pollution and health effects from locally emitted and transnationally transported biomass combustion aerosols’, 27-28 October 2005, Helsinki, Finland. Organisers: Raimo O. Salonen and Marko Vallius.

International ERAC-symposium 'Exposure, health effects and risk assessment of metals in the environment', 24 October 2007, Kuopio, Finland. Organisers Raimo O. Salonen and Marko Vallius.

Suomalaisten altistuminen kemiallisille aineille ja säteilylle –seminaari [Exposure to chemicals and radiation in Finland - seminar], August 30-31, 2006, Helsinki, Finland.

4.4.3 TV- or radio programmes

Pro Healthy Life, Multimedia on Environmental Health, CD-ROM, about 1500 pages, 2002, partially based on previous TV-program on environmental health (6 sessions of 30 min. each).

TV series on food, a 30-min session on food safety (among 6 sessions), utilized widely for continued education.

TV programme on PM research at KTL in 2003 (YLE Teema 30 min).

Expert consultations in drafting dietary recommendations concerning contaminants of fish (given by the Food Safety Agency of Finland).

MOT, TV-program on misunderstood risks, December 2006, Jouko Tuomisto and Paolo Mocarelli interviewed e.g. on dioxin risks.

Elämä pelissä (Life at stake), TV-program on good life and promoting healthy lifestyle, with accompanying book with the same name, ed. by J. Huttunen and P. Mustajoki, Chapters Ympäristö on iso asia, pp. 199-211 (Environmental health is an important issue) and Carpe diem – nauti elämästä, elä kohtuudella, pp. 259-262 (Carpe diem – enjoy life, live in moderation) by Jouko Tuomisto, Kustannus Oy Duodecim 2007, 262 p.

5 PROGRESS AND RESULTS OF THE RESEARCH

5.1 Highlights of dioxin research

Using our experimental model based on dioxin sensitivity differences among Han/Wistar (Kuopio; H/W) and Long-Evans (Turku/AB; L-E) rat strains and further developed rat lines A, B and C we were able to characterize two types of endpoints for dioxin toxicity. Type I endpoints are mainly low dose endpoints (liver CYP1A1 activity, thymus weight, tooth defects, many developmental defects), and they are independent of genotype variation (dioxin resistance alleles). Type II endpoints (mortality, weight loss, liver toxicity, serum bilirubin) are mainly high dose effects, and their efficacy is suppressed by the dioxin resistance alleles. Classification criteria between type I and type II effects have been established.

In molecular biological studies on dioxin toxicity we largely focused on characterizing the influence of TCDD on mRNA and protein expression in one of its major target tissues, the liver. These studies were mainly carried out in liaison with Prof.Allan B. Okey's team (Univ. of Toronto, Toronto, Canada). Applying DNA microarrays and AH receptor knockout (AHRKO) mice we obtained strong support for the view that the AH receptor (AHR) plays an essential role in a wide variety of physiological processes in addition to acting as a central mediator of dioxins' effects, since almost as high a number of liver genes (392) were affected by AHR status alone (in the absence of exposure to any AHR ligand) as were responsive to TCDD (456). Novel findings included e.g. downregulation of metallothionein, CYP2B20 and CYP17a1, and dramatical upregulation of the serine proteinase inhibitor, SerpinA12, expression by AHR. Furthermore, we discovered that in AHR-wildtype mice, TCDD dramatically induces mRNA expression of estrogen-related receptor gamma, potentially antagonizing the action of ERα and ERβ. These findings help delineate the extent and identities of genes influenced by AHR and dioxins.

In a collaborative study with Dr. Allan B. Okey's and Dr. Roberta Pastorelli's teams (Instituto di Ricerche Farmacologiche "Mario Negri", Milano, Italy) we simultaneously examined dioxin-induced alterations in hepatic mRNA and protein expression levels using microarrays and mass spectrometry-based proteomics coupled with our rat model (two strains with an over 1000-fold sensitivity difference to acute lethality of dioxin). Significant changes in the abundance of several proteins were recorded. These could be divided into 3 classes based on their dependence on rat strain

and dioxin exposure: 1) TCDD-independent and exclusively strain-specific (e.g. disulphide isomerase A3, regucalcin), 2) strain-independent and only dependent on TCDD exposure (e.g. aldehyde dehydrogenase 3A1, Se-binding protein 2), and 3) dependent on both TCDD exposure and strain (e.g. oxidative stress-related proteins, apoptosis-inducing factor). Furthermore, computational search for regulatory elements showed that the changes mainly stemmed from the transcriptional level. Some of these differential responses may play a role in the uniquely wide strain sensitivity difference and thus give insight into the mechanism of acute dioxin toxicity.

In the third microarray study, we examined whether TCDD-induced down-regulation of hepatic gene expression could be mediated by the recently discovered group of important regulatory molecules, microRNAs (miRNAs), evolutionarily conserved, small noncoding RNA molecules that regulate gene expression at the level of translation. We used two miRNA array platforms as well as quantitative RT-PCR to measure miRNA levels in wildtype vs. *Ahr*-null mice and in dioxin-sensitive L-E rats vs. dioxin-resistant H/W rats as well as in rat 5L hepatoma cells and mouse Hepa-1 hepatoma cells in culture. Treatment with TCDD in vivo caused few changes in miRNA levels in mouse or rat livers and those changes that were statistically significant were of modest magnitude. Hepatoma cells in culture also exhibited few changes in miRNA levels in response to TCDD. AHR genotype had little effect on hepatic miRNA levels, either in constitutive expression or in response to TCDD. Therefore, it is unlikely that mRNA downregulation by dioxins is mediated by miRNAs nor are miRNAs likely to play a significant role in dioxin toxicity in adult rodent liver.

A key method in our studies on molecular mechanisms of dioxin toxicity has thus been genome-wide analysis of gene activity changes by microarrays. As an independent means for verification of the data obtained by microarray analysis, we have employed quantitative real-time RT-PCR. To yield accurate and reliable information, this method relies on normalization of the data with an indifferent “house-keeping” gene (or a couple of such genes). Since dioxin affects the expression of a myriad of genes, we undertook screening of 18 commonly applied normalization genes for their usefulness in dioxin-treated rats. This approach revealed that extreme care is indeed needed in selecting proper normalization genes for the set purpose, since most of the genes studied were influenced by dioxin or feed restriction (a necessary additional control measure in short-term dioxin experiments). However, we were able to pick up two genes whose expression remained stable throughout the experiments (*Pgk1* and *GAPDH*).

At the molecular level, the exceptional TCDD resistance of H/W rats is mainly based on a single protein: the AHR. In H/W rats, there is a single-nucleotide polymorphism (G→A) at the first base of intron 10. This results in disruption of the normal exon/intron junction and usage of cryptic splice sites with the formation of 3

mRNAs, two insertions and one deletion. Since the insertions yield the same translational product, there are two novel AHR proteins, both restructured at the C-terminal transactivation domain. Using isoform-specific probes we found that the TCDD-resistant H/W rats only express the mutant forms of the AHR with the insertions representing about 85% of total expression. In contrast, the TCDD-sensitive strains express almost exclusively the wild-type AHR. All these 3 rat AHR forms (wild-type and both variants) have now successfully been transferred to AHR knockout mice, and they have been found to exhibit high expression levels. A pilot study implied that one of the variants (insertion variant) affords resistance to mice against cholangiohepatitis and mortality caused by high doses of TCDD. Thus, the new animal model holds great promise as an effective tool for analyses of dioxin toxicity mechanisms and for elucidation of AHR structural features critical for dioxin sensitivity.

In studies addressing the brain as a potential target of TCDD, we used c-Fos as a neuronal activity marker in an immunohistochemical experiment on dioxin's possible effects on hypothalamic nuclei established to be involved in regulation of food intake and body weight. No major changes were detected suggesting either that the time-point chosen (day 1, light hours) was too early (or at an incorrect time of day) or that hypothalamus is not a primary target for dioxin. However, in a separate study we demonstrated that all the essential elements for AHR-mediated dioxin signaling are expressed in the hypothalamus and they are functional as evidenced by a rapid and pronounced induction of CYP1A1, CYP1A2 and AHRR in response to TCDD exposure. Further support for involvement of the CNS in TCDD toxicity was obtained in a related project in which we analysed by quantitative real-time RT-PCR the impact of TCDD on mRNA levels for numerous hypothalamic neuropeptides and their receptors regulating feed intake and body weight. TCDD turned out to modulate a wide variety of feeding-related factors although its main effect was targeted at orexigenic transmitters and receptors.

In two other collaborative studies we examined the effects of TCDD on *p53* tumor suppressor gene and on salivary glands. Together with Prof. Johan Högberg's team (Karolinska Institutet, Stockholm, Sweden) we were able to show that TCDD seems to impair the *p53* response to DNA damage by reducing p53 protein and Ser15-phosphorylated p53 levels via the AH receptor (AHR). TCDD brought about these effects at least in part by increasing basal protein levels of the p53 counteracting molecule, Mdm2. The attenuated *p53* response to a variety of genotoxic and cytotoxic agents deprives the cells of an important defence mechanism and thus may play a role in TCDD-induced carcinogenesis. Finally, in collaboration with Dr. Pirjo-Liisa Lukinmaa's group (Univ. of Helsinki, Helsinki, Finland) we found that dioxin exposure impaired epithelial branching and cleft formation in cultured mouse E13 submandibular

salivary glands. Auxiliary experiments with EGF and fibronectin implied reduced EGF receptor signalling underlying the impact of dioxin.

Our studies have confirmed that developmental defects are more sensitive and more relevant endpoints of dioxin toxicity than cancer, and that genetic factors (the dioxin resistance alleles) play a only a minor role in determining individual susceptibility to low dose developmental defects as compared with high dose and short-term endpoints of dioxin toxicity. In our experimental models developmental molar defects were the most sensitive endpoints, followed by impairment of male reproductive system and bone toxicity. Prenatal period was shown to be the critical window of sensitivity for these effects, which emphasizes the importance of *in utero* exposure. For the molar development the critical developmental event is from tooth initiation to early bud stage, and the likely target is dental epithelium. We also showed that TCDD exposure increases the sensitivity of rat offspring to caries at very low maternal doses, and that this phenomenon is not associated with relative changes in the enamel mineral composition. The use of molar teeth and bones as biomarkers for dioxin exposure was investigated in bank voles and field voles living in contaminated former sawmill area. Molar teeth proved to be a robust and useful biomarker for exposure to dioxin-like compounds.

We have further characterized developmental effects of TCDD on bone geometry, mineral density and mechanical strength after perinatal exposure, and the TCDD tissue concentrations associated with these changes. It is plausible that altered retinoid metabolism is associated with TCDD-induced developmental defects, because the decrease of the levels of the newly identified retinoid metabolite 9-cis-4oxo-dihydro retinoic acid followed the similar dose-response relationships as developmental defects.

Effects of TCDD on bone development was also studied using bone marrow mesenchymal stem cells cultured in conditions promoting differentiation to bone forming osteoblasts or to bone resorbing osteoclasts. Differentiation was monitored by analysing sequentially the appearance of differentiation markers characteristic for the main phases of differentiation: proliferation (RUNX2), matrix maturation (APHOS), and mineralization (osteocalcin, calcium concentration). TCDD exposure did not affect cell proliferation, but resulted in inhibited increase in expression of APHOS and osteocalcin as well as inhibited mineralization. Inhibition of osteocalcin expression proved to be very sensitive to TCDD as subpicomolar concentrations (100 fM) resulted in significantly decreased expression. TCDD-treatment also concentration dependently induced the expression of AHR repressor (AHRR), which indicates that the AHR signalling pathway is fully functional. Studies in Ahr-null mice suggest that the effects of TCDD on osteoblast differentiation are mediated via AHR pathway. However, the effect of TCDD is not a direct effect of gene expression, because both APHOS and osteocalcin genes lack dioxin responsive elements (DREs) in their regulatory sequences.

Studies in bone marrow stem cells differentiating into bone resorbing osteoclasts indicated that also this differentiation process is highly sensitive to dioxins.

We also characterized TCDD-induced alterations in the proteome profile of differentiating osteoblasts. Preliminary findings suggest that after 3 culture days TCDD deregulates the expression of proteins linked to early steps of osteoblast proliferation and differentiation, including cytoskeleton, matrix structures and cell metabolism proteins. After 7 culture days of TCDD exposure, TCDD (i) evokes a coordinated up-regulation of oxidative pathways (beta-oxidation, the Krebs cycle, the electron transport chain); (ii) may impair calcium homeostasis and possibly mineralization trough the action of anexin1, involved in intracellular Ca^{2+} binding; (iii) triggers a change in the expression of cytoskeleton proteins suggesting an alteration in cell plasticity.

Comparison of acute toxicity syndromes of TCDD and 1,2,3,4,7,8-hexachloro-dibenzo-p-dioxin (HxCDD) in TCDD resistant H/W rats as well as in rat lines A and B revealed highly different outcome of toxicity. Unexpectedly, HxCDD was more potent than TCDD and resulted in rapid loss of body weight in all rats studied. HxCDD also caused gastrointestinal hemorrhage and pale (fatty) livers in H/W and line A rats. In line B rats HxCDD caused pronounced hepatic fatty degeneration, whereas TCDD induced hepatic accumulation of biliverdin and its derivatives. These findings suggest that in addition to the classical AHR mediated pathway, HxCDD possesses an AHR-independent mechanism of toxicity characterized by rapid body weight loss, mortality, fatty liver and gastrointestinal hemorrhage.

Using a case-control design and individually estimated dioxin exposure data we were able to show that soft tissue sarcoma risk does not increase due to current exposures to dioxin. The unique study measured dioxins, furans, PCBs, and other contaminants from more than 500 patients. The data are well suited for further on-going research on determinants of exposure. Together with collaborative data from Seveso and from Finnish high-risk population groups, and from our experimental studies, these have given new possibilities to assess the risks of cancer and developmental effects associated with dioxins.

Material from the case-control study has also been useful for estimating the exposure of general population to dioxins and PCBs. By far the most important correlation was to age, i.e. both dioxins and PCBs are gradually accumulating over the whole lifetime. This is very important for the distribution of risk. As developmental effects are the most important outcome for risk assessment, the most important population subgroup is young mothers. Their dioxin and PCB concentrations are quite low and also have been declining over the last 30 years. The most important source in Finland is Baltic fish.

5.2 Highlights of fine particle (PM) research

5.2.1 Exposure

Already in the early phase the PM exposure studies resulted in several interesting findings concerning individuals not exposed to tobacco smoke. (i) Personal $PM_{2.5}$ exposure was found to be closely associated with ambient concentrations mainly during leisure time, but not during the workdays and commuting. (ii) Population $PM_{2.5}$ exposures levels turned out to be close to ambient $PM_{2.5}$, but their compositions differ considerably, traffic exhaust particles and mineral dust particles contributing in average two times more to personal than ambient $PM_{2.5}$. (iii) The probabilistic $PM_{2.5}$ exposure model, based on hourly ambient air concentrations, penetration of $PM_{2.5}$ from outdoor to indoor air, contributions of indoor sources and personal time-microenvironment-activity data, predicts remarkably accurately the personal exposure distribution of the population. The model is readily applicable for risk assessments and policy evaluations. (iv) PM source reconstruction is a powerful tool for an in-depth analysis of the distributions of individual exposures to $PM_{2.5}$ from different sources separately for exposures at home, at work, outdoors and in traffic. (v) Even quite modest passive exposure to tobacco smoke in average doubles the total $PM_{2.5}$ exposure level.

In the European ULTRA study, outdoor levels of $PM_{2.5}$ and absorbance (blackness of the particulate matter, an indicator of its inorganic carbon (= BC) or soot concentration) were found to be major determinants of personal and indoor levels. Traffic was also an important determinant of absorbance while cooking was associated with increased levels of both absorbance and $PM_{2.5}$.

Based on the source apportionment analysis, over half of the ambient air fine particle concentration in Helsinki was from long range transport, c.a. 20% from traffic, 10% from soil and sea salt, and the rest from other local combustion sources.

Source attribution of ambient air $PM_{2.5}$ in Helsinki, Basle and Athens using structural equation modeling demonstrated that in the absence of lead in petrol, it is almost impossible to distinguish between the primary exhaust particles from traffic and combustion particles from many other sources. Besides, particularly in locations like Basle, traffic emitted particles form a significant and equally undistinguishable fraction of the particulate matter originating from outside of city and country. Otherwise, crustal, secondary, oil combustion and salt particles are clearly recognized.

On-road $PM_{2.5}$ concentration was measured using a mobile laboratory van in Helsinki. Relative to fixed site urban $PM_{2.5}$, street air concentrations of Cu, black

carbon (BC), Fe, and Zn in $PM_{2.5}$ were elevated. Since considerable amount of time is spent in the traffic, the high on-road concentrations of traffic related pollutants can contribute significantly to the exposure to BC and several transition metals.

Particulate air pollution in buses and trams in Helsinki was investigated in co-operation with Finnish Institute of Occupational Health, University of Helsinki, Helsinki Metropolitan Area Council, and Finnish Meteorological Institute. Elevated $PM_{2.5}$ concentrations were observed inside the buses. In particular, the BC concentration was higher in vehicles compared with the Helsinki background air measurement stations. The average particulate mass and number count concentrations were higher in the cabin compartment than in the driver's compartment. Furthermore, newer technology, i.e. the newer models of the tram and bus, seemed to reduce drivers' exposure to both particle number and mass concentrations. Fine PM inside the vehicles was enriched with several transition metals.

The $PM_{2.5}$ samples collected in the Helsinki subway system showed very high concentrations of several metals, most importantly iron. Based on a rough estimate, commuting via the subway in Helsinki adds only 3 % to $PM_{2.5}$ exposure, but nearly 200 % to the exposure of iron in $PM_{2.5}$, and 60 and 40 % to the exposures of Mn and Cu, respectively.

Analyses of the studies on PM exposures in traffic within the WHO coordinated HEARTS study in Leicester, UK, and Florence, Italy, revealed interesting findings. In Leicester where the traffic PM exposures of schoolchildren walking and in car on way to school were simulated and real time ultrafine PM, $PM_{2.5}$ and $PM_{10\text{-}2.5}$ (the coarse PM fraction) monitored, the traffic impact was striking for ultrafine PM counts, notable for the coarse PM, but quite weak for $PM_{2.5}$. No correlations were found between any of the short term in-traffic concentrations between these three particle size fractions. Yet, ultrafine PM did constitute an identifiable fraction of the $PM_{2.5}$, and another fraction of the $PM_{2.5}$ was distinguished as belonging to the road dust PM. In conclusion, of all PM size fractions, $PM_{2.5}$ appears to be the one most weakly associated with local traffic emissions. In Florence, however, where the $PM_{2.5}$ exposure concentrations in busses and taxis were compared to simultaneously monitored urban background concentrations, the levels in traffic were found to exceed the urban background by 20..30 g/m3. As a rule off thumb, it was concluded that ca. ½ of the total traffic PM exposure occurs in traffic, while waiting for transport, or while walking, driving or riding in public transport.

Three indoor factors were resolved in the indoor $PM_{2.5}$ source apportionment: re-suspension, K-factor and Cu-factor. High longitudinal outdoor-indoor correlations for secondary sulfate and urban mixture and the fact that the indoor-generated $PM_{2.5}$ was

not related to ambient concentrations support the use of fixed site $PM_{2.5}$ as a surrogate for personal exposure to ambient fine particles in epidemiological time-series studies.

A panel study was conducted among 48 ischemic heart disease patients in November 2005 – May 2006 in Kotka as part of the 'Inflammation and particulate matter' (HIPPU)–project in co-operation with Kymenlaakso University of Applied Sciences and Finnish Meteorological Institute. Preliminary results on the $PM_{2.5}$ exposure show that cooking, candle burning, use of spray and ironing can lead to high short-term $PM_{2.5}$ exposure. However, only 20 % of the reported activities lead to observable peaks in exposure. The average effect of the reported indoor activities on 24h exposure concentration was in general low. Although there was large variation between the participants, to majority of them, exposure to outdoor-generated particles in the home was the most important source of exposure. Thus, indoor sources need to be taken into account especially when studying the health effects of short-term $PM_{2.5}$ exposures. During the episode of long-range transported particles from forest fires in western Russia at the end of April and beginning of May 2006, the $PM_{2.5}$ exposure was over 3-fold compared to the average exposure.

A probabilistic model for the prediction of fine PM exposure distributions within a target population was developed and validated. Although modeling of individual short term fine PM exposures has in international studies turned out to both demand very much data and produce poor prediction accuracy, much simpler probabilistic modeling of population exposure distributions turned out to predict the true exposure distribution remarkably accurately.

5.2.2 Toxicology

The EU-funded PAMCHAR project, co-ordinated by KTL, we started in 2002 a laboratory calibration, field testing and subsequent modification of a Harvard high-volume cascade impactor (HVCI) to enable large capacity samplings of the ambient air coarse, fine and ultrafine PM for toxicological studies in a comparable manner to the low-volume reference samplers commonly used in detailed chemical and source characterisation of the size-segregated PM samples. In a pilot study in August-September 2002, we performed an exercise of thorough chemical and toxicological characterisation of a major PM episode during long-range transported wildfire smoke-haze in Helsinki and developed standard operating procedures (SOPs) for a European-wide use of the HVCI technique.

Subsequently, the validated HVCI and reference sampling techniques were used in sampling campaigns of six European cities with contrasting geographical and seasonal

features and local emission sources (2002-2003) as well as in Helsinki during four seasons (2003-2004). Overall, $PM_{10-2.5}$ samples had a higher inflammatory activity than $PM_{2.5-0.2}$ and $PM_{0.2}$ samples in the mouse macrophage cell line RAW264.7, but $PM_{2.5-0.2}$ samples showed the largest differences in inflammatory activity, and $PM_{0.2}$ samples in cytotoxicity, between the sampling campaigns. $PM_{0.2}$ sample from wintertime Prague with proven impacts from local coal and biomass combustion had very high cytotoxic and apoptotic activities and caused a distinct cell cycle arrest. $PM_{2.5-0.2}$ samples from wintertime Prague had also the highest genotoxic activity in the human respiratory epithelial cell line A549. In the lungs of healthy mice, exposed intratracheally and lavaged 4, 12 and 24 hours thereafter, $PM_{10-2.5}$ samples had a somewhat higher and longer-lasting inflammatory activity than $PM_{2.5-0.2}$ samples. $PM_{0.2}$ samples showed negligible inflammatory activity. Similarly to the in-vitro studies in macrophage cell line, there was more heterogeneity in the inflammatory responses to $PM_{2.5-0.2}$ samples than to $PM_{10-2.5}$ samples between the sampling campaigns. In both the macrophage cell line and the mouse lung, $PM_{2.5-0.2}$ samples from springtime Barcelona and summertime Athens had the highest inflammatory activities. The other three sampling campaings were conducted in autumntime Duisburg, wintertime Amsterdam and springtime Helsinki.

Further studies were conducted on the inflammatory and cytotoxic effects of the water-soluble and -insoluble as well as organic-solvent-soluble and -insoluble fractions of the very same $PM_{2.5-0.2}$ and $PM_{10-2.5}$ samples in the 264.7 mouse macrophage cell line. The toxic effects were associated mainly with the water-insoluble particulate fractions.

The latest study results from the PAMCHAR-EU project have suggested that photochemically oxidized organic compounds and transition metals (most consistently Ni and V), especially from fuel oil combustion, contributed to the inflammatory activity of $PM_{2.5-0.2}$ samples in both the mouse macrophage cell line in vitro and the mouse respiratory tract in vivo. In addition, the soil-derived particulate compositions (Ca^{2+}, Al, Fe, Si) contributed to the inflammatory activity of $PM_{2.5-0.2}$ samples, but their role in $PM_{10-2.5}$ samples was not so obvious due to a possible role of mostly undefined biogenic material. Long-range transported secondary inorganic ions (NO^{3-}, NH^{4+}, SO_4^{2-}) had either negative or inconsistent association with the inflammatory activity of $PM_{2.5-0.2}$ samples. Interestingly, poor biomass and coal combustion were associated with elevated levels of PAHs and a consistent negative impact of $PM_{2.5-0.2}$ samples on the inflammatory activity, possibly due to an immunosuppressive effect. Overall, our study results support previous epidemiological findings that the local sources of incomplete combustion and resuspended road dust have a key role in urban air particulate pollution -related health effects.

In the HIPPU project, we tested the inflammatory activity and cytotoxicity of ultrafine ($PM_{0.2}$), fine ($PM_{2.5-0.2}$) and coarse ($PM_{10-2.5}$) particulate samples in the macrophage cell line. The samples had been collected with the HVCI in connection to a 24-week epidemiological panel study among elderly subjects with ischemic heart disease in Kotka. These results will be subsequently combined with the results on inflammation and coagulation markers in blood of the patients.

The PUPO-health project investigated the toxicological characteristics of ultrafine ($PM_{0.2}$), fine ($PM_{1-0.2}$ and $PM_{2.5-1}$) and coarse ($PM_{10-2.5}$) particulate samples emitted from normal and poor operation of one masonry heater. The toxic properties of wood smoke particles were connected to the emission measurements by the Fine Particulate Technology Laboratory of the University of Kuopio and the chemical characterization of the particles made by the Finnish Meteorological Institute (FMI). Particulate emissions from smouldering combustion (restricted combustion air) had several-fold higher inflammatory activity and cytotoxicity than those from normal combustion, when the test results were calculated per emitted cubic metre of air or produced energy unit. The particulate samples from smouldering combustion produced cell death and DNA fragmentation at a lower mass dose than those from normal combustion.

The FINMERAC project made an integrated health and environmental risk assessment of toxic metals, especially nickel and copper, in a large industrial complex of nickel and copper smelters and nickel refinery in Harjavalta. We examined the reliability of metal analysis made from archived PM_{10} filter samples of 1992–2005 and tested the feasibility of the use of these samples in toxicological in vitro tests for inflammatory, cytotoxic and genotoxic activity.

5.2.3 Epidemiology

An association was shown for the first time between ultrafine and fine particles with risk of myocardial ischaemia as indicated by electrocardiogram changes. Fine particles were also associated with increased epithelial barrier permeability and cardiorespiratory symptoms. We have also performed source apportionment of $PM_{2.5}$ in Helsinki during two winters and have now been able to link source specific $PM_{2.5}$ with respiratory and cardiovascular end points. The results show the importance of $PM_{2.5}$ from combustion, especially traffic.

Among adult asthmatics in the European ULTRA study, the negative effects of $PM_{2.5}$ on respiratory function were most strongly associated with particles originating from local combustion, although long-range transported particles also had an effect. We

found that the same $PM_{2.5}$ sources were responsible for the increased risk of exercise induced ischemia among persons with coronary heart disease.

We analyzed associations of source-specific $PM_{2.5}$ and $PM_{2.5}$ -absorbance, an indicator for combustion originating particles, with logarithmized values of urinary CC16, a marker for lung damage in three cities Helsinki, Amsterdam and Erfurt. The results suggest that $PM_{2.5}$ from combustion sources increases epithelial barrier permeability in lungs.

In another European multi-centre study, the HEAPSS study, we found evidence that particulate air pollution is associated with cardiovascular hospitalisations both in the most Southern and Northern parts of Europe, although e.g. the levels of ultrafine particles were found to differ by a factor of five between the two areas. Traffic originating air pollution was associated with increased risk of hospitalisation for first myocardial infarction. In the cohort of myocardial infarction survivors, air pollution increased cardiac hospital readmissions.

In Helsinki, we have one of the longest time-series of fine and ultrafine particles. Using this data in time-series studies we found evidence that especially $PM_{2.5}$, but also ultrafine particles and CO, are associated with increased risk of fatal stroke in short term among the elderly (>65), but only during the warm season. The report was published in the leading journal, Stroke. Present analyses focus on asthma and COPD emergency room visits, and respiratory hospital admissions, and mortality. Particles form traffic source were strongly associated with children's asthma visits with 3-5 day lag. Asthma and COPD visits of the elderly were associated with same day levels of fine particles, CO, NO_2, and secondary particles. Fine particles, even at low levels, are also associated with hospital admissions for all respiratory diseases, COPD and pneumonia among people aged over 65 years.

In the multi-centre EU project RUPIOH, we found evidence that measurement error in epidemiological time-series studies assessing exposure at a central site may be higher for particle numbers than for fine particle mass/specific components. Furthermore, the results indicated that (i) neither particle mass nor fine particle absorbance can be used as a surrogate to assess the exposure to particle number; (ii) the degree of which the ambient air concentrations from fixed sites can be used to assess exposure vary for different parameters and urban areas and; (iii) regardless of site location and characteristics, emissions from vehicles is an important source of particle number and to a lesser extend of particle absorbance and mass concentrations. Although a central site could not assess absolute concentrations across the urban areas for particle number, measurements at the central site reflected the temporal variation for all particle indices at the selected homes across the urban area.

Another EU project (AIRGENE) assesses whether systemic inflammation is a major mechanism of air pollution effects and possible gene-environment interactions. First results indicate an immediate response to particle number concentrations on the interleukin 6 (IL-6) level, possibly leading to the production of acute phase proteins, as seen in increased fibrinogen levels. This might provide a link between air pollution and adverse cardiac events. First analyses with genetic polymorphisms have been started.

In 2007, the HIPPU panel study (see above) was in the data management and analysis phase. Associations between the personal exposure to particulate air pollution and the measured health parameters (inflammation and blood coagulation markers etc.) are being analyzed. In the future, we aim to compare the time-series of inflammatory responses observed among humans with the inflammatory activity of the collected particulate samples in a macrophage cell line.

Wildfires in Eastern Europe in 2002 as well as in 2006 increased periodically $PM_{2.5}$ concentrations in Finland for several weeks. The observed air quality was poor, while at the same air quality index did not properly indicate this. KTL (i) investigated the reasons for this mismatch, (ii) estimated the potential number of daily mortality associated with the exposures, and (iii) used time-series epidemiology techniques to compare the toxicity of the wildfire particles with that observed in more general urban PM studies. The 2-week average increase in the population (3.4 million) exposure to $PM_{2.5}$ was 15.7 μg/m³. Assuming 1% RR per 10 μg/m³ as observed for urban $PM_{2.5}$, the additional mortality was 17 cases (estimated lower and upper estimates 8-34 cases).

5.3 Highlights of risk analysis research

Risk analysis was planned as the main theme of the Centre. This research is being conducted at two different levels. First, it is tightly built in to all projects in dioxin and PM research, which aim at providing relevant material for risk assessment in all their activities. Second, risk analysis research focuses on the actual methods of doing risk assessment.

The main goal was to develop decision-relevant, comprehensive examinations on particular environmental health risks. This required the combined ability to describe complicated risk situations in an explicit way and to do detailed quantitative modelling of specific areas of relevance. We therefore started to actively develop our expertise in several methods used in risk benefit and other analyses, including value of information, Bayesian methods, and expert elicitation. For all this work, close collaboration with other groups and, within the Centre, regular researcher meetings proved invaluable.

The work on Open Risk Assessments became the main focus of research during the years 2006-2007. The main areas of development were on methods to involve large

groups of interested people in making an assessment. To enable this, there is a need to develop a flexible information structure, set practical rules for the process, and offer user-friendly platforms to perform risk assessments. We have made good progress in all of these areas. Several internal reports distributed within projects were being transformed into research articles in the end of the CoE period.

Several important research projects and some of their outcomes are briefly described here, roughly in the order of starting date.

We participated in several PM risk assessment projects. One of them was on traffic (Composite traffic), one on all emissions in Finland (KOPRA), and one on the main local sources, namely wood combustion and traffic (PILTTI). The emissions, dispersion, exposure, and health effects were studied in an integrated way. We also estimated intake fractions for fine particles in a unique study that took into account also atmospheric chemistry and explored particle size dynamics. Intake fraction proved useful by providing practical estimates for source-specific exposure to be used in decision modelling. As partners in an international study, we utilised expert elicitation (a formal interview method to elicit the estimates and uncertainties when measurements are not possible) for estimating total effects and differential potencies of fine particles, as the contemporary uncertainties had high policy implications.

The research is done mainly in co-operation with Finnish Environmental Institute and Finnish Meteorological institute. The main results from the projects were presented in November 2007 in stakeholder meeting that gathered broad spectrum of participants. Several articles have been published and will be published based on these results.

For dioxins, we effectively utilized our in-house expert group for rapidly scrutinising the hotly debated environmental health issue about contaminants in farmed salmon in 2004. In this work, we effectively used value of information (an estimate of the cost caused by the remaining uncertainty in the decision situation), and systematically used this tool further to evaluate uncertainties and research needs in our risk analyses. Bayesian statistical methods were explored in studying dioxin time trends in the Baltic area.

Few research groups have tried to understand science-policy interface, i.e. the interplay of scientific, or causal, connections and policy development and decision-making. Our contribution in this area strengthened especially through our work in the European air pollution network (AIRNET), where the width of our expertise was seen in the fact that only KTL, in addition to the coordinator, had members in all five working groups.

An EU project Intarese (years 2005-2010) about environmental health risks has been the main arena for methodology development. Our research group is involved in

most critical workpackages related to method development, namely, exposure-risk assessment, risk characterization, cross-cutting issues, and toolbox specification. The toolbox is an ambitious software development project for making integrated risk assessments.

In Intarese we are also involved in a few case studies, the largest contribution relates to traffic. Our traffic research has been focused on composite traffic (a novel alternative, a large-scale demand-responsive public transportation) research. The main question is the interaction of the current public transportation and the hypothetical composite traffic.

Our research group is coordinating another EU project Beneris (years 2006-2009). This project has done very close collaboration with Intarese. The work on combining dose-responses from epidemiology and toxicology is an example of this. In addition, we have collaborated with the Delft University of Technology on Bayesian models and expert elicitation. Research on comparative risks of fish consumption and dioxins in fish has continued as part of the Beneris project. The risk model was especially developed to estimate risk-benefit ratios for different fish species based on Finnish concentration and consumption. This work has now expanded also to cover risks of methyl mercury.

The collaboration between KTL, the University of Kuopio, and the Geological Survey of Finland actively continued in the ERAC network (Environmental Risk Assessment Centre, years 2005-2007). Finmerac project (years 2006-2008) studies health and environmental risks due to metal emissions around three industrial sites in Finland. These are the industrial parks of Harjavalta and Kokkola, and the Pyhäsalmi mine. Our role is to perform integrated risk assessment models about these cases, and based on these results develop generalizable methods and models for metal risk assessments. This work is ongoing, and it has given us a lot of experience in performing Open Risk Assessments in practice.

HiWATE (years 2007-2010) is a newly started EU-project on health risks of disinfection by-products and microbial contamination in drinking water. The role of our group in HiWATE is to provide methods for risk.benefit analysis. HiWATE is also interlinked with the water case study in Intarese.

Heimtsa (years 2007- 2011) is another new EU-project that has connections with Intarese. It is a broad project on environmental health risk assessment, utilising integrated methods. The role of our group in Heimtsa is mainly to observe and assist utilisation of the risk analysis methods that are also being developed in Intarese.

6 SPECIFIC SIGNIFICANCE OF FUNDING FROM THE FINNISH PROGRAMME FOR CENTRES OF EXCELLENCE IN RESEARCH

The specific importance of Academy funding was apparent, as the funding continuously increased the multidisciplinary collaboration within the Centre. As in most environmental health areas, the most important aspect was the true interdisciplinary collaboration within a project, giving a highly fertile and beneficial soil for wider understanding of environmental health problems. This was true both of scientific innovation and also doctoral and postdoctoral education. Achieving this required a stable and relatively long-lasting financial background, and therefore their utilisation to the full extent was only possible in a funding system like this Centre of Excellence project.

The interdisciplinary discussion was crucially important in the present Centre, as one of the major aims of the Centre was to improve risk analysis methods. Therefore, in addition to collaboration e.g. in field works or experiments, focusing on improving risk analysis methods provided a challenging context and platform for new innovation. Therefore, multidisciplinary collaboration did not take place only within fine particulate research teams (exposure-toxicology-epidemiology) or the dioxin research team, but also crossing the border between fine particulate matter and dioxin studies.

7 DEVELOPMENT OF COLLABORATION

Research teams of the Centre are and have been highly active within the European Union Framework Programmes as coordinators and partners of multinational research projects. Partially overlapping, Dioxin risk assessment contract was co-ordinated 2000-2003. During the period 2002-2004, the Centre co-ordinated a major multicentre toxicology project on ambient air PM (PAMCHAR) and was a partner in 10 projects (AIRGENE, HEAPSS, PHEWE, APHEA-II, RUPIOH, HEARTS, FUMAPEX, EXPOLIS-Index EXPORED, BONETOX) funded by the European Commission Fifth Framework Programme.

With regard to fine particulate exposure studies, different European centres have had highly standardized SOPs, many originally developed at KTL, to compare outcomes and to increase the power of the study. The first study of this kind was the EXPOLIS study, in which several centres in Europe used identical study design, equipment and SOPs. This led to our participation in two new EC 5th Framework

Programme funded multicentre collaborative research programmes. The first was WHO coordinated HEARTS project, where the health risks of exposure to urban traffic generated air pollution, noise and accidents were evaluated and modelled in three European cities, Florence, Italy, Lille, France and Leicester in the UK. The air pollution exposure measurements relied largely on equipment and protocols developed at KTL, and population exposure modelling based on probabilistic simulation developed at KTL (in collaboration with RIVM, Bilthoven, the Netherlands). The second one was the DTU (Copenhagen, Denmark) coordinated FUMAPEX project which aimed at developing and validating air pollution exposure models for urban level episode risk assessment and management. Also there the KTL developed exposure simulation technique was used.

KTL also was a partner in one CEFIC/LRI funded project, and coordinated another. The former, EXPOLIS-Index was coordinated by University of Basel in Switzerland, and the other partners included University of Southern California in Los Angeles and UC Berkeley in California, and Imperial College in London. It brought further the analyses of exposure influencing time activity patterns, statistical source apportionment of exposure and the determination of intake fractions for urban indoor pollution sources. The latter, ExpoFacts was coordinated by KTL and had 12 European partners including EC/JRC/IHCP Ispra, and WHO/Euro in Bonn. It created a European wide database of exposure factors for probabilistic exposure and risk modelling needs, and a website, where this database and its background materials can be freely browsed, searched, and from which the original data can be reorganised and downloaded for exposure and risk modelling needs (see http://www.ktl.fi/expofacts). New funding was acquired to keep this database updated and operating, and to initiate the next steps in its further development.

With regard to air pollution epidemiology, SOPs were introduced to the European air pollution epidemiology community by the ULTRA projects coordinated by KTL in 1997-2001. This work lead to our participation in practically all the 5th Framework Programme EU projects on air pollution epidemiology, especially those concerning ultrafine particles. In the HEAPSS study, there were four European research groups besides us (GSF, Neuherberg, Germany; IMIM, Barcelona, Spain; ASL RM E, Rome, Italy; Karolinska Institute, Stockholm, Sweden). In the AIRGENE study, all the HEAPSS countries were included, but also Greece (University of Athens). In the RUPIOH study, our partners were the University of Athens, IRAS (Utrecht) and RIVM (Bilthoven) from the Netherlands, and the University of Birmingham, UK. Department of Physics in the University of Helsinki collaborated with us in all the EU-projects.

In 2002-2004, similar developments were made in the PAMCHAR project on the new high volume cascade impactor sampling of several particulate fractions for

extensive chemical characterization and toxicological testing. In this EU-funded project, coordinated by KTL, there were four principal partners (RIVM, University of Dusseldorf, University of Utrecht, Finnish Meteorological Institute) and 7 other collaborating research institutes from a total of seven countries.

In dioxin studies, on the other hand, all partners had completely different but complementary study areas. Thus, for instance, clinical tooth development studies from other centres were compared with our animal toxicity studies. These collaborations gave us extra strength and opened far wider possibilities for risk analysis than would have been possible based on our own database only.

Another important collaboration in dioxin studies was with the University Toronto on utilisation of microchip technology for mapping comparative gene expression in our differently sensitive rat lines. We continued our collaboration with the Department of Anatomy and Cell Biology, University of Oulu, and Institute of Environmental Medicine, Karolinska Institute in bone studies and dioxin toxicology, as well as with the University of Wisconsin in Madison in developmental toxicity studies on male reproductive effects. We also established a new collaboration on proteomics with the Mario Negri Institute for Pharmacological Research in Milan, Italy, and collaboration on retinoid metabolism with the Department of Food Toxicology, School of Veterinary Medicine.

We actively developed contacts to other research groups working on risk assessment in environmental health in Europe. A major result of this contact development was an application of an EU integrated project. The application was submitted in fall 2004, and it was accepted in 2005. This is a large research project with 32 institutes from all over Europe, and the Centre has several key roles especially in workpackages related to risk assessment methodology.

By 2006, most projects of the 5th Framework Programme had ended, but in 2006 the Centre was still a partner in 5 projects (HEARTS, BONETOX, AIRGENE, PHEWE, ENVIE). The 6th European Union Framework Programmes has mostly lacked research on environmental health, but has had a major emphasis on risk assessment. In 2006, the Centre was funded coordination of one STREP-project (BENERIS) and a partnership in ATHON (Assessing the toxicity and hazard of non-dioxin-like PCBs present in food). Moreover, the Centre is a central partner of a major integrated project (INTARESE, total budget 12 million €) on risk assessment. INTARESE is a large research project with 32 institutes from all over Europe, and the Centre has several key roles especially in work packages related to risk assessment methodology. These new collaborations will increase significantly our European collaboration and visibility in the field of environmental health risk assessment. The latest additions to international collaboration are EU-projects Heimtsa and HiWATE. Heimtsa is a broad project on

environmental health risk assessment, utilising integrated methods and HiWATE is a newly started EU-project on health risks of disinfection by-products and microbial contamination in drinking water

The Centre has had active collaboration with Harvard Center for Risk Analysis and Delft University of Technology. For example, the expert elicitation project on fine particle risks has been done in collaboration with them. As described above, other collaboration extended to the United States (Univ. of Wisconsin in Madison, Harvard School of Public Health), Canada (Univ. of Toronto) and Japan (Univ. of Okayama).

Within Finland, Centre has significantly increased collaboration with the Geological Survey of Finland and the University of Kuopio through establishing a new Environmental Risk Assessment Centre (ERAC) with funding from TEKES. The Centre is also leading a Graduate School on Environmental Health that will fund 5 postgraduate positions for the years 2006-2009.

8 PUBLICATIONS OF THE CENTRE FOR ENVIRONMENTAL HEALTH RISK ANALYSIS 2002 - 2007

All original articles published in international peer-review journals can be found in alphabetical order in the Appendix.

8.1 Original articles and reviews in international peer – review journals

8.1.1 Fine PM – Exposure assessment

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APPENDIX

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