

Forskningsprogram			
SNAP <input checked="" type="checkbox"/>		REPROSAFE <input type="checkbox"/>	
FLIPP		Inriktning: Ekonomiska styrmedel <input type="checkbox"/>	
		Inriktning: Informationssystem och indikatorer IPP <input type="checkbox"/>	
Projekttitel (svensk): Hjärt-kärl- och luftvägseffekter av experimentell exponering för oxidativ och partikulär luftförorening			
Projekttitel (engelsk): Cardiovascular and respiratory responses after experimental exposure to oxidative and particulate matter air pollution			
Huvudsökande	Efternamn: Sandström	Förnamn: Thomas	Födelseår: 1957
	Kvinna <input type="checkbox"/> Man <input checked="" type="checkbox"/>		
	Organisation: Lung- och Allergiklinikens forskningsavd		Institution: Folkhälsa och Klinisk Medicin, Umeå Universitet
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Medsökare	Efternamn, förnamn, tjänst, organisation, institution: Blomberg Anders, DrMed, Foass, Lung och allergiklinikens forskningsavd, Folkhälsa och Klinisk Medicin		
	Telefon: 090-7852234	E-post: anders.blomberg@lung.umu.se	Kvinna <input type="checkbox"/> Man <input checked="" type="checkbox"/>
<p>1/ Projektets betydelse för programmet Detta projekt är inriktat mot programmets målsättningar vad gäller studier av biologiska mekanismer bakom hälsoeffekter av luft-föroreningar och hälsoeffekter studerade i både singel och kombinerade luftföroreningsmodeller.</p> <p>2/ Miljörelevans och förväntad betydelse för miljöpolitiken Projektet är avsett att ge en ökad biologisk och toxikologisk kunskap om bakgrunden till hälsoeffekter inom luftvägar och det kardiovaskulära systemet av oxidativa och partikulära luftföroreningar, ge indikationer om hänsyn bör tas till kombinationseffekter av olika luftföroreningar.</p> <p>3/ Mål för projektet är att med hjälp av humanexperimentella modeller klarlägga om kombinationsexponering med ozon och dieselavgaser förstärker effekter på luftvägar och de kardiovaskulära systemet. En projektdel inriktas mot att klarlägga den lokala arteriovenösa inverkan dieselavgaser på endotelaktivering och koagulation mätt in-vivo på försökspersoner, kombination med kompletterande mätningar av systemeffekter. Med hjälp av en nyutvecklad partikel-instillationsmodell på människa tar vi steget vidare från in-vitro djurförsök inom EU-projektet HEPMEAP genom att instillera utvalda partikelprover, samlade i europeiska trafikmiljöer och som visat sig ha speciella, oxidativa och arachidonsyre-metabolit-genererande kapacitet. Via den humanexperimentella modellen försöker vi klarlägga lokala immuneffekter människa och validera de tidigare använda modellerna. Därtill fördjupas vår mekanistiska forskning under projektet beträffande signaltransduktion på kinas- och transkriptionsfaktor -nivå i bronkslemhinnebiopsier från diesel- och ozonförsök för att detaljerat klarlägga via vilka mekanismer som hälsoeffekterna medieras.</p> <p>4/ Metodik och genomförande Denna grupp använder väletablerade exponeringskammare för dieselavgaser och ozon tillsammans med bla bronkoskopier, analyser av lungsköljvätska, biopsier, blodprover, Holter-EKG samt en underarms-modell av kärl- och koagulations-aktivering, inom ramarna för ett väl etablerat mångårigt internationellt samarbete.</p> <p>5/ Kommunikationsinsatser Projektets resultat kommer att redovisas för SNAP såväl som nationella och internationella myndigheter, internationella konferenser och publiceras i vetenskapliga tidskrifter.</p>			
		År 2004	År 2005
		1 051 166,-	1 051 166,-
Summa sökta medel per år i kr:			

Miljöforskningsnämnden
Ansökan om projektbidrag inom Naturvårdsverkets forskningsprogram

Sökta projektmedel fördelade på kostnadslag	År 2004 (kr)	År 2005 (kr)
Personalkostnad inkl. soc. avgifter * Ester Roos-Engstrand, lab-ing, 6 mån heltidsarbete, 34 781,- per mån Annika Johansson, forskningssköterska, 6 mån heltidsarbete, 30 600,- per mån Jamshid Pourazar lab-ing, 6 mån heltidsarbete, 34 781,- per mån	208 686,- 183 600,- 208 686,-	208 686,- 183 600,- 208 686,-
Övriga omkostn exkl moms (förbrukningsmtrl, analyser, resor etc)** Kostnader för drift av exponeringskammare för dieselavgaser respektive ozon, analyskits, antikroppar, kemikalier och förbrukningsvaror	250 000,-	250 000,-
Delsumma av ovanstående poster:	880 972,-	880 972,-
Förvaltningspåslag: 20 %	170 194,-	170 194,-
Totalsumma per år: (införs sid. 1):	1 051 166,-	1 051 166,-

*) Specificera namn, tjänst **) Specificera

Samtliga övriga miljörelaterade projekt för vilka de sökande har beviljats anslag eller söker anslag för 2004-2006. OBS Även EU-finansiering.

Projekttitel	Finansiär	Tidsperiod	Sökt kr	Beviljat kr
HEPMEAP Experimentella studier av luftvägs- och kärleffekter	EU Hjärt-lungfonden	2001-2004 2004-2006	340 000,-/år 1 297 000,-/år	340 000,-/år

**Miljörelaterade projekt för vilka sökande har beviljats anslag för 2000-2003
 OBS Även EU-finansiering**

Projekttitel	Finansiär	Tidsperiod	Beviljat Kr
HEPMEAP	EU-FP5	2001-2004	1 020 000
Ett flertal experimentella luftföroreningsprojekt	Ett flertal nationella och utländska finansiärer	2000-2003	Totalt 10 925 137,-

Datum och sökandes underskrift, vilken samtidigt ger Naturvårdsverket tillåtelse att publicera sökandes namn på sin webbplats:	Datum och underskrift av prefekt eller motsvarande med namnförtydligande:
Umeå 2003-10-14	Umeå 2003-10-14 Bengt Järholm, prefekt

Ansökan skall bestå av detta formulär jämte högst sex sidor lång projektbeskrivning på **engelska** (strukturerad som den svenska sammanfattningen samt en redovisning av kunskapsläget). Referenser till egna publikationer ges med sifferhänvisning till CV. Andra referenser ges i löpande text. Sökandes och eventuell medsökandes CV får omfatta högst två sidor. Inga bilagor kommer att beaktas vid bedömningen. Ansökan (max 10 A4-sidor, 12 punkters teckenstorlek) skall inlämnas i **original + 15 kopior samt elektroniskt** till ansok@naturvardsverket.se. Häfta ihop ansökan och använd hålat papper. Ansökan skall ha inkommit senast den 15 oktober 2003 till Naturvårdsverket, Forskningssekretariatet, 106 48 STOCKHOLM.

Miljöforskningsnämnden
Ansökan om projektbidrag inom Naturvårdsverkets forskningsprogram

Cardiovascular and respiratory responses after experimental exposure to oxidative and particulate matter air pollution

Project leader: Professor Thomas Sandström, Department of Respiratory Medicine and Allergy, University Hospital, Umeå, Sweden.

Co-applicants: Anders Blomberg, M.D. Ph.D. Ragnberth Helleday, M.D. Ph.D., Maj-Cari Ledin, Research Engineer, Jamshid Pourazar, Research Engineer, Research Fellow, Jenny Bosson, M.B. Research Fellow, Håkan Törnqvist, M.D. Research Fellow.

1. The project's role and significance for the programme

The present proposal is given in response to Call 3 of October 15, 2003 of the Swedish National Air Pollution and Health Effects Programme (SNAP).

The experimental research here proposed is part of the long series of the experimental air pollution research by the applicants and their international collaborators for more than 15 years. It is directed to give a strong response to some important key aspects in the research area of respiratory and cardiovascular toxicological responses to air pollution. The proposal therefore adheres to several aims of the SNAP-call for proposals 2003:

“to study the impact of health outcomes in both single and multi pollutant models”,
” to elucidate some biological mechanisms for an association between air pollution and various health outcomes” and “to clarify mechanisms of effects of air pollution”.

2. Environmental relevance and expected significance for environmental policy

Air pollution is associated with significant adverse health effects and it is important to determine the biological effects in the airways, vascular endothelium, blood coagulation and on heart function. An increased toxicological and mechanistic knowledge of air pollution effects has been requested by authorities such as EU, WHO and EPA in order to achieve a better understanding of the compelling epidemiological data showing a range of adverse health effects. Additionally, the possible interaction between particulate matter (PM) and gaseous pollutants such as the strong oxidant ozone has been claimed important to clarify. This is of value for interventive actions for traffic and other combustion sources, as well as for the national and European authorities regulatory activities.

3. Objective and hypothesis.

Hypothesis: The Overall Hypothesis is that particulate air pollution induces acute inflammatory and reactive effects in the airways and in the cardiovascular system, leading to the adverse health effects identified in healthy subjects as well as people with respiratory diseases like asthma and COPD, as well as cardiovascular disease, as reported in a multitude of epidemiological studies.

Objective: To study the inflammatory and oxidative stress effects in the airways and cardiovascular system by ozone and diesel engine exhaust, as well as particulate matter sampled from ambient air in European traffic situations, with the intent to achieve an increased mechanistic and toxicological understanding of the adverse health effects associated with these air pollutants.

Specific scientific objectives:

- To elucidate whether a pre-exposure with ozone enhances the pro-inflammatory, respiratory, cardiovascular and systemic effects of diesel engine exposure, the following day.

- To study cardiovascular effects by diesel engine exhaust, as regards the local arterio-venous endothelial activation and coagulation balance in humans (measured in the forerarm blood vessels) together with Holter-ECG analyses of disturbed cardiac electrophysiology.
- To use a newly developed endobronchial particle instillation model in humans to study oxidative stress and inflammatory effects caused by ambient environmental fine and coarse particles collected within the EU HEPMEAP project, and clarify whether the airway responses in humans in-vivo are coherent with the corresponding data from in vitro and animal tests within this project.
- To mechanistically study the role the signal transduction pathways and transcription factor activation in the bronchial epithelium as regulators of diesel exhaust and ozone induced reactive and inflammatory responses.

4. Methods and performance

Ozone–diesel exhaust interaction

The important question on whether gaseous oxidative pollutants such as ozone potentiates airway and systemic effects of particulate matter has been put forward by WHO, EU, EPA and other authorities. Apart from the mechanistic and immunological aspects, a potentiating or modulating effect could indicate the need of a new approach for interpretation of air pollution health effects data and suggest the need of balanced exposure limits, taking into account the interaction of two or more pollutants together.

Based on data from a large series of ozone and diesel exhaust exposure studies, we intend to expose 25 healthy subjects to ozone 200 ppb/filtered air in the afternoon of day one. In the morning of day two, this is followed by diesel engine exhaust exposure with 100 µg PM/m³ or filtered air. Bronchoscopy with bronchial mucosal biopsies and BAL is performed six hours after the diesel/air exposure. This is a time point where we have earlier demonstrated inflammatory ozone effects to have ceased and bronchial mucosal neutrophilia not yet established after this level of diesel exhaust exposure, but an increased IL-8 expression being present in the airway mucosa.

We postulate that: A/ “pre-exposure with ozone followed by diesel exposure” gives a significantly enhanced neutrophilic inflammation in the bronchial mucosa” compared with B/ “Air exposure followed by diesel exposure” and C/ “Air exposure followed by air exposure”. The theoretical fourth leg with “ozone exposure followed by air exposure” is not to be included, as four exposures with bronchoscopies per person is not practically possible, while our experience with three exposures is positive. Importantly, we have already earlier documented the effects of “ozone exposure followed by air exposure” (Blomberg 1999, Mudway 2001, Stenfors 2002). Bronchial mucosal biopsies are to be sampled followed by quantification of the inflammatory cell infiltration, changes in vascular adhesion molecule expression, T-cell differentiation, bronchial epithelial cytokine expression, proliferation and apoptosis. Signal transduction pathways are determined with methods well established in our lab. Bronchoalveolar lavage is analysed for antioxidants and detailed lung function measurements are performed together with sampling of breath condensate and exhaled nitric oxide (eNO). As we are also focused on cardiovascular effects, blood samples are analysed for changes in the coagulation cascade and endothelial activation and Holter-ECG is recorded for analyses of disturbances in the electrophysiology and homeostasis.

Endobronchial particle instillation

Within the HEPMEAP-project co-ordinated by the applicant, ambient particle samples have been collected with “High Volume Slit Impactors” on several sites in Europe with contrasting contribution from motor vehicles including diesel and gasoline engines. While the study codes are not broken, the in-vitro tests have demonstrated large differences in oxidative and arachidonic acid generating effects. Ragnberth Helleday in our lab has developed a model with particle instillation inspired by earlier allergen provocation models with endobronchial instillation. Dose response pilot studies in healthy subjects have demonstrated a clear

neutrophilic influx at six and eighteen hours after bronchial instillation of ambient European PM as compared with the NaCl diluent. In groups of 15 subjects, we intend to study the coherence from the in-vitro and animal work which has characterized the biological reactivity of these PM and selected high and low reactive PM for comparisons. Additionally “fine” and “coarse” PM from the same sites are compared, in order to challenge the hypothesis that the majority of the biologically reactive capacity lies with the fine and ultra fine particle cuts. Additional information on the HEPMEAP project can be found at www.hepmeap.org.

Endothelial activation and influence on the coagulation system by diesel exhaust

We have during the last year established a collaboration with the group of Dr David Newby, Cardiologist and British Heart Foundation Lecturer on particulate air pollution effects on the local vasculature as regards endothelial activation and locally increased coagulability. Newby has established a model where an ultra-thin arterial needle is inserted in arteria radialis and venous canulae are inserted in v. mediana cubiti and arterial infusion is performed with drugs in order to study the endothelial activation and coagulation by sequential venous samples (Newby 2002, Kemme 2003, Chia 2003). The Edinburgh group have established that tobacco smoke is able to double the local coagulation activity. We will now use the diesel engine exhaust exposure model with diesel/filtered air exposures to study local and systemic vascular effects in groups of 15 subjects. This will be followed by studies in healthy elderly people as well as people with established cardiovascular disease.

Signal transduction and cell activation in the airways by ozone and diesel

In order to understand how the airways and cardiovascular system is affected by these pollutants we are studying the mechanistic steps of cell activation following inhalation to dissect and follow the subsequent reactive local and systemic effects. This is done within the PhD projects of J Pourazar who has demonstrated increased TH2 cytokine expression in the airway epithelium after diesel challenge, and that it is initiated through the MAPk p38 pathway with supportive p65 NFkB and AP-1 nuclear translocation in the epithelium. This has been presented as invited lectures at ATS and ERS this year. He is continuing to analyse complementary cell initiation steps including p44/p46 MAPk (ERK), JNK1,2 and EGFR in new and archived diesel biopsies. In parallel Jenny Bosson from Berkley, Ca, is focusing her PhD programme on the corresponding questions on how ozone induced cell activation in the airways involves different steps of signal transduction and is mediated via different expressions of cytokines. Her research has further supported the hypothesis that asthmatic subjects respond with a different Th2 cytokine, and neutrophil chemoattractant driven bronchial epithelial response as compared with healthy subjects (Bosson 2003).

Methods

Exposure techniques. Diesel engine exhaust exposures are performed in the exposure chamber established at “Svensk Maskinprovning” in Umeå, whereas for the ozone exposures the exposure chamber at “Arbetslivsinstitutet Umeå” is used. For particle instillations via bronchoscope, we use PM samples from the EU HEPMEAP-project that have been extensively characterized for physical and chemical characteristics as well as in-vitro and in-vivo animal oxidative and pro-inflammatory properties. 250 µg of particles are diluted in NaCl. Instillations of different PM are compared with instillations of diluent only and the segments are re-visited at 18 hours when biopsies for immunohistochemistry and bronchial wash measurements of antioxidants and inflammatory mediators are performed.

Bronchial mucosal biopsies. Bronchoscopies are performed with biopsies according to a well established protocol sampled and processed in glycolmetacrylate for immunohistochemistry and liquid nitrogen for PCR. Inflammatory cell markers such as EG2, tryptase, neutrophil elastase, CD3, CD4, CD8, CD25, CD68, epithelial cytokine expressions IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-17, IL-18, GRO α , TNF α , GM-CSF, ENA-78 as well as adhesion molecules ICAM-1, VCAM-1, E-selectin and P-selectin. Kinases and transcription factors are

stained and nuclear translocation is established for MAPK family, ERK, NFkB, AP-1, c-Jun, c-Fos. Epithelial proliferation, EGFR and apoptosis is determined. The majority of the measurements are done in Umeå with the PCR analysis of cytokines done in Southampton.

Bronchial wash (BW) and bronchoalveolar lavage (BAL) are performed with measurements of antioxidants such as glutathione, urate, ascorbic acid, alpha-tocopherol as assayed by Prof F J Kelly, Kings College, London. Inflammatory mediators such as tryptase, methyl-histamine, MPO and fibronectin are done together with MMP-6, MMP-9. Cell pellets are assayed for gene expression with PCR at King's College London.

Blood samples. Standard blood differential counts, CRP, electrophoreses, fibrinogen are assayed. Antioxidants assayed in London and the coagulation cascade analysed in the haematology lab by Prof Cedric Hermans in Brussels.

Lung function measurements are performed with a whole body plethysmograph.

Holter ECG:s are recorded during 24 hours with our Danica equipments and analysed in Edinburgh for arrhythmias, ST- and RR variability with dynamic QT-compensation.

Forearm model for determination of endothelial activation and influence on the coagulation system. Following the insertion of an ultra-thin arterial needle in the brachial artery an saline infusion is started. Acetylcholin, substance-P and nitroprusside are used to release t-PA via different pathways which are characterized. A series of venous samples are taken from the bilateral v. mediana cubiti before and during each infusion and characterized for local release of t-PA, PAI-1, CRP, IL-6, TNF α and IL-1 receptor antagonist as well as the rheological blood condition. These measurements are done over six hours after both diesel exposure and filtered air, which as always are performed blinded in randomized sequence.

5. Communications in relationship to the programme

The results from the project will be widely disseminated through documentation in the final report to SNAP, as well as presentations at international seminars and conferences, international publications in peer-review journals and direct communications with Naturvårdsverket, EU, AIRNET and WHO.

6. Scientific background

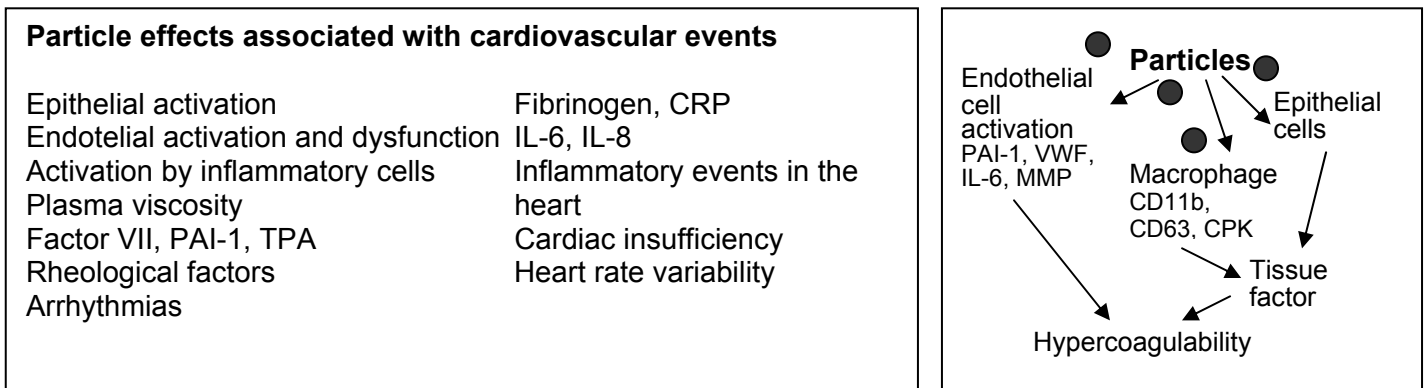
Health effects due to air pollution arising from motor vehicles and other combustion sources have become an important public and political issue worldwide. While the gaseous oxidative pollutants clearly are of concern, much focus has been directed towards particulate matter (PM) pollution and various health effects including deterioration of cardiovascular and respiratory diseases with increases in symptoms, lung function changes, rescue medication need, emergency room admissions, hospitalisation and mortality (Dockery et al, New Eng J Med 1993, Nyberg and Pershagen, Scand J Work Environ Health 2000). While the sources and composition of the PM pollution may vary at different places and time to time, diesel engines remain important sources of airborne particles as they may emit up to 10-100 times more particles compared with gasoline engines. Over more than a decade the applicants have performed a series of well cited experimental human studies evaluating diesel induced biological effects in humans, as reviewed together with animal and in vitro studies (Sydbom 2001, which was the 3rd most cited paper in ERJ the following year). The symptomatic and bronchoconstrictive effects have been described together with systemic inflammation with thrombocytosis, inflammatory cell activation and migration into the bronchial mucosa and epithelium as well as airway spaces reflected with bronchoalveolar lavage and induced sputum (Salvi 1999, 2000, Nordenhäll 2001). Interventive aspects with a ceramic particle trap on the tail pipe as well as intervention with combined active coal/particle filter for car cabins have been performed (Rudell 1996, 1999).

Asthmatic subjects have from epidemiological studies been suggested to be more susceptible than healthy to air pollution. The applicants have reported to the US Health Effects Institute (HEI), based on their funding of the project, that asthmatics indeed differ

from healthy subjects as regards cytokine expression in the bronchial epithelium following diesel engine exhaust exposure 100 µg/m³. Furthermore this results in a pronounced increase in their bronchial hyperresponsiveness measured by metacholine test. Most recently we have conducted the largest experimental diesel engine exhaust exposure project so far with over 60 individuals exposed to diesel exhaust 100 µg/m³ and filtered air within the EU supported HEPMEAP programme. The series of experiments clearly confirmed that diesel engine exhaust with 100 µg PM/m³ yielded a neutrophilic inflammatory response in healthy subjects of a magnitude suggesting that the response would be present at much lower concentration. Asthmatics treated with β₂-agonists only demonstrated a significantly different response to healthy, again suggesting the asthmatic airway inflammatory status to be an adverse factor in the response to PM air pollution.

Most recently, the generous support from the SNAP programme has enabled the applicants to perform a similar study in subjects with COPD and an age matched elderly control group. The full data sheet will be available later during the autumn, well in time for the official report. As submitted as abstract to the 2004 American Thoracic Society meeting, the subjects with COPD responded to the diesel engine exhaust with an airway inflammatory response in induced sputum contrasting them even from asthmatics in terms of enhanced neutrophilic migration, which could suggest both additional tissue damage and exacerbation of the COPD inflammation. Additionally, it was found that healthy non-smoking elderly individuals also responded with an airway inflammation, thereby contradicting the assumption that elderly would be less prone to respond to PM pollution. The very detailed characterisation of the coagulation cascade, as well as 48 hour Holter ECG:s are currently under analysis.

Cardiovascular effects of PM pollution, including diesel exhaust is of major concern. The demonstration that diesel particles actually penetrate into the vascular system (Nemmar 2002) and may provoke a thrombosis formation in blood vessels is compelling (Nemmar 2003). Therefore the mechanistic aspects of PM pollution on the inflammatory cascades, coagulation factors and vascular endothelial activation have most recently come into focus, as we have recently addressed in review format (Sydbom 2001).



7. Time schedule.

The applicants have been active in the experimental air pollutant research arena for more than 15 years and have a track record to keep study time lines and reporting times to the Swedish, European and American Funding Bodies that have kindly supported the research. We have built an organisation with several senior scientists, well trained and motivated staff as well as having a steady flow of Ph.D. students, enabling us to organise and perform experimental air pollution research according to strict time lines. Projects will be run partly compartmentalised and partly with overlap regarding staff and scientists. We have found this to be effective and result in a large productivity and effective use of staff, fellows and scientists. All methods and techniques are set up and ready to be used by the Umeå group and our European colleagues Profs AJ Frew and ST Holgate Southampton, Prof FJ Kelly King's College London, Prof Cedric Hermans Brussels and Dr D Newby Edinburgh.

Additional collaboration and support is found within the HEPEAP projects 9 collaborating groups. Particle instillations will start early 2004. The diesel forearm measurements of endothelial and blood effects will include time course tests during spring 2004, with the majority of experiments during late summer and autumn of 2004. The ozone-diesel project is run during autumn 2004 – mid spring 2005. The experimental series is followed by intense analysing periods. This ensures that the reporting time demanded by SNAP will be met.

8. Rational for the economical plan

Exposure studies at this level and magnitude is laboursome and demands a considerable number of staff, fellows, physicians and lab resources. We have considerable costs for the running of the exposure chambers. This is based on national and international research support. The large HEPMEAP project has a 1.3 million Euro total support which stretches into 2004. It covers only a fraction of our lab costs, but has been instrumental in developing a fruitful international collaborative network. We have several other funding bodies who have given valuable support over the years.

The current amount applied for to SNAP is clearly realistic and indeed covers only a part of the financial support need to run the experimental models developed. As can be seen from the economical report the air pollution lab has had a turnover of over 3 million SKr annually over the last years, distributed from several different national, European and overseas funding bodies

Over the years we have had many foreign research fellows spending time and doing research together with us. For the vascular studies Nick Mills registrar in cardiology and research fellow will be doing the measurements in our lab, based on the UK research support covering his salary, equipment and travel.

9. Selected pre-2001 references relevant to the application

(2001-2003 references are given with CV)

- Rudell B, Sandström T, Stjernberg N, Kolmodin-Hedman B. Controlled diesel exhaust exposure in an exposure chamber: Pulmonary effects investigated with bronchoalveolar lavage. *J Aerosol Sci*, 1990, 21, suppl 1, 411-414.
- Rudell B, Sandström T, Hammarström U, Ledin M-C, Stjernberg N. Evaluation of an exposure set-up for studying effects of diesel exhaust in humans. *Int Arch Environ Health* 1994, 66, 77-83.
- Rudell B, Ledin MC, Hammarström U, Stjernberg N, Sandström T. Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. *Occup Environ Med* 1996 53,658-62
- Salvi S, Blomberg A, Rudell B, Kelly FJ, Sandström T, Holgate ST, Frew AJ. Acute inflammatory response in the airways and peripheral blood following short term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999;159:702-709.
- Rudell B, Wass U, Hörstedt P, Levin JO, Lindahl R, Rannug U, Sunesson AL, Östberg Y, Sandström T. Efficiency of automotive cabin air filters to reduce acute health effects of diesel exhaust in human subjects. *Occup Environ Med*. 1999 Apr;56(4):222-31
- Rudell B, Blomberg A, Ledin M-C, Lundbäck B, Stjernberg N, Hörstedt P, Sandström T. Bronchoalveolar inflammation following exposure to diluted diesel exhaust: effects of filtered vs. unfiltered exhaust. *Occ Environ Med* 1999, 56,4,221-231.
- Salvi SS, Nordenhäll C, Blomberg A, Rudell B, Pourazar J, Kelly FJ, Sandström T, Holgate ST, Frew AJ. Acute exposure to diesel exhaust increases IL-8 and GRO- α production in healthy human airways. *Am J Respir Crit Care Med*, 2000;161:550.
- Mudway IS, Blomberg A, Frew AJ, Holgate ST, Sandström T, Kelly FJ. Antioxidant consumption in nasal lavage fluid following exposure of healthy subjects to ozone. *Eur Respir J*, 1999,13,1429-1438.
- Blomberg A, Mudway I, Nordenhäll C, Hedenström H, Kelly FJ, Frew, Holgate ST, Sandström T. - Ozone-induced early airway inflammatory and antioxidant responses not correlate with lung function decrements. *Eur Respir J*, 1999, 13, 1418-1428.
- Krishna MT, Madden J, Teran LM, Biscione GL, Lau LC, Withers NJ, Sandström T, Mudway I, Kelly FJ, Walls A, Frew AJ, Holgate ST. Effects of 0.2 ppm ozone on biomarkers of inflammation in bronchoalveolar lavage and bronchial mucosa of healthy subjects. *Eur Respir J* 1998,11,1294-300.

CV for Project Leader Thomas Sandström

TS (born in 1957) received his MD in 1983 and presented his PhD thesis on Respiratory effects of the air pollutants sulfur dioxide and nitrogen dioxide at in 1989. Two years later in 1991 he was awarded an associate professorship at the Medical Faculty at Umeå University and become specialist in Respiratory Medicine the same year.

In 1992 TS received a Senior Lecturer/ Consultant position and in 1997 he was awarded the first Chair in Respiratory Medicine at Dept of Respiratory Medicine and Allergy at Umeå University Hospital

TS has tutored six fellows to PhD's (Five on air pollution and one on asthmatic airway inflammation) and currently tutors five more fellows. He has been examiner ("opponent") on eight PhD Theses since 1997. He serves and has served on several Committees, Steering Groups and Boards nationally, in Europe and the US. He is currently engaged in WHO work groups on air pollution issues. In 2001 he was awarded the Swedish Royal Skytteanska Research Prize.

The applicant is co-ordinator for the EU FP5 supported project HEPMEAP and participant in the EU supported Thematic European Air Pollution Network (AIRNET) which is under final financial negotiation. Together with Prof G Viegi Pisa he did in 2001 arrange the EU sponsored AFORDEE meeting, an EU-US interactive meeting on "Air Pollution Effects in the Elderly". TS is Associate Editor for European Respiratory Journal and European representative in the American Thoracic Society (ATS) Environmental-Occupational Health Program Planning Committee. He has repeatedly served as Chairman and invited speaker at European and American Respiratory, Allergy and Air pollution Meetings and during the last year in this respect been invited to the Fraunhofer Institute 8th International Inhalation Symposium, California Air Pollution Technology and Solutions Management Meeting, Ontario Air Pollution Control Meeting, Canada, and other meetings.

Scientific papers in peer review journals during the last 3 years: 2001- Sept 2003

1. Frew AJ, Salvi S, Holgate ST, Kelly F, Stenfors N, Nordenhäll C, Blomberg A, Sandström T. Low Concentrations of Diesel Exhaust Induce a Neutrophilic Response and Upregulate IL-8 mRNA in Healthy Subjects but Not in Asthmatic Volunteers. *Int Arch Allergy Immunol* 2001;124(1-3):324-5.
2. Mudway IS, Stenfors N, Blomberg A, Helleday R, Dunster C, Marklund SL, Frew AJ, Sandström T, Kelly FJ. Differences in basal airway antioxidant concentrations are not predictive of individual responsiveness to ozone: A comparison of healthy and mild asthmatic subjects. *Free Rad Biol Med*, 2001;31(8):962-74.
3. Midulla F, Strappini P, Sandström T, Bjermer L, Falasca C, Capocaccia P et al. Cellular and noncellular components of bronchoalveolar lavage fluid in HIV-1-infected children with radiological evidence of interstitial lung damage. *Pediatr Pulmonol* 2001;31(3):205-13.
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