MID-TERM REPORT OF THE SAPALDIA GRANT – SCIENTIFIC PART
(Swiss National Foundation Grant No 33CSCO-108796; April 2006 through March 2008)

2. Study data

2.1. Executive summary

2.1.1. Key aspects of the study design and statistics

SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults) is a multi-center study started in eight geographic areas representing the range of environmental, meteorological and socio-demographic conditions in Switzerland. This study was initiated in 1991 with a follow-up assessment in 2002. In 1991, 9'651 subjects, aged 18 to 60 years, were recruited for a detailed interview and more than 90% of them underwent lung function and atopy tests. In the 2002 follow-up 8'047 participants provided health information, of these 6'528 underwent a physical re-examination, repeating the same measurements as in 1991 and 6'345 participants provided blood samples, enabling the establishment of an extensive blood, plasma, serum and DNA bank. In addition, 1'813 subjects aged 50 and older participated in 24h-ECG Holter monitoring to provide detailed data on parameters of heart rate variability as an early marker of cardiac response to the environment.

2.1.2. Work performed and findings

Supported by previous grants, analysis of the data collected at SAPALDIA 1 and 2 surveys (i.e. in 1991 and 2002) has produced about 40 peer-reviewed papers between 1994 and August, 2006. The aim of the present grant was to pursue intensively the analysis of the data provided by the first two surveys of the cohort in order to set the stage for a third survey that could occur in 2009-2010. Thus, this mid-term report will focus on new publications and the development of new national and international collaborations. Data on methodology and implementation of the cohort have been published in details earlier. Maintenance of the cohort was performed through updating the address data base during the period of the current grant.

Two major achievements have been made possible by the present grant that are directly related to the original objectives of the SAPALDIA cohort. Firstly, a paper validating our prediction model for individual exposure to PM_{10} (particles of < 10 μm of aerodynamic diameter), a crucial instrument for further research in the field, has been published,[9] and another paper on a prediction model for individual exposure to NO_2 has just been submitted.[18] Secondly, we could publish a paper in the *New England Journal of Medicine* demonstrating for the first time in a longitudinal study that outdoor air pollution is associated with the evolution of individual lung function in adults.[10]

The complexity of air pollution exposure assessment made it mandatory for SAPALDIA to collaborate in this field of research on an international level. Thus, SAPADIA is co-applicant of several European projects among which is the ESCAPE project that has just been granted by the Framework Programme 7 of the EU (see section 3.1).

The study of gene-environment interactions is a major objective for SAPALDIA with its collection of blood samples for DNA and other biomarkers from the majority of study subjects. The present grant has made possible the publication of two association studies of single nucleotide polymorphisms (SNPs) with the long term evolution of lung function parameters and respiratory health in the Swiss population.[4,11] Papers in preparation will explore further associations including environmental factors, in particular outdoor and indoor air pollution.

Association studies of genetic markers with clinical outcomes in single cohorts have been criticized because of the risk of chance findings and lack of reproducibility in other populations. As for exposure assessment, it was mandatory for SAPALDIA to participate in consortia that allow cross-validation of genetic associations, and also to participate in costly genome-wide scans of the DNA samples. As a nested project of the present grant, SAPALDIA collaborated with the ECRHS (European Community Respiratory Health Survey) on the association of genetic variation of TNF-alpha with asthma-related

phenotypes.[16] Moreover, SAPALDIA has become a partner in two different international consortia conducting genome-wide scans for asthma and lung function (see 3.2).

The SAPALDIA cohort also represents a unique opportunity to study determinants of respiratory and cardio-vascular health in the Swiss population. Second-hand smoke is an important problem of public health that has been addressed by three major papers supported by the present grant.[3,6,8] Determinants of asthma and COPD have been the focus of several papers of the present grant,[1,12,14,15,17] as well as the interaction between obesity, cardiac and respiratory parameters at the population level.[13]

Finally, the address data base of the participants has been transferred from Lausanne to Geneva and it is now hosted by the University of Geneva. The update of all addresses has been performed at the end of 2007 in collaboration with a specialized contractor as well as by manual updates. It will be completed by a news letter to the participants by April, 2008.

2.2. Background

Population-based cohort studies offer a unique opportunity to assess the importance of environmental, behavioral and genetic factors for public health and morbidity in the population. The scientific value of the cohort grows with increasing time of follow-up and with each additional health assessment.

2.3. Aims and Objectives

The primary aim of the SAPALDIA cohort study is the study of the evolution of respiratory and cardiovascular health (including morbidity and mortality) in its ageing cohort with special considerations to: air pollution exposure, tobacco smoke exposure (both active and passive), occupational exposures, genetic and molecular characteristics, sex- and gender-related factors, past health status and behavioral risk factors.

2.4. Methodology of implementation

The size of the original study population (N=9651) had been chosen such as to provide the statistical power necessary to address important hypotheses regarding cross-sectional associations between respiratory parameters and air pollution exposure. Extensive power calculations were also performed before the second survey and had shown that the size of the cohort population (N=8047) was sufficient to address important questions on longitudinal changes in respiratory health parameters and their relation to air pollution exposure history. Moreover, long term effects of air pollution on mortality can be assessed with sufficient statistical power in the next 5 to 10 years. The statistical power of SAPALDIA to successfully address important scientific hypotheses regarding morbidity will increase as long as the accelerated increase in the proportion of subjects with specific health problems offsets the steady loss to follow-up.

Inclusion/exclusion criteria: please, refer to 2.1.1. Outcomes: please, refer to 2.1.1.

Biases that arise from the statistical correlation of factors (i.e., confounding) can be addressed analytically using multiple regression models.

Biases related to differential non-participation or loss to follow-up are more difficult to address. We use weighted regression analyses and data imputation techniques to address these problems, while being well aware that it is impossible to correct all the biases associated with missing information.

Strategies adopted to ensure optimal compliance: SAPALDIA has 14 years of experience in following its cohort and maintaining contact with its study participants. Based on this experience, measures to ensure optimal follow-up has resulted in a retaining rate of 82% in SAPALDIA 2. We continue these follow-up measures which comprise: i) regular mailings to participants with newsletters ii) regular

updates of addresses by the company DCL Data Care in Lucerne iii) strategic use of local media (newspapers/TV/Radio) iv) periodical validation of address information by comparison with records at local registries v) linkage with mortality records from the Federal Office of Statistics.

Biological specimen and environmental data collected: maintenance of an up-to-date file of available blood fraction and DNA aliquots at the bio banks in Zürich and Geneva. We have also held regular meetings with local, regional, and national air monitoring agencies to coordinate the maintenance of air pollution monitoring sites and acquisition of required data.

Strategies to allow third party access: the server of the ISPM Basel harbours the complete health and exposure database in SAS-format in different pass-word protected directories. Moreover, a separate partition of the server contains copies of the major data sets used for statistical analyses by internal and external researchers. In collaboration with SAS Inc., we are in the process of installing a software package including a wide range of Web-functionalities. This enables the development of a web-based system for external clients to access the database via the Internet and to perform queries and simple statistical analyses.

Ongoing or new national/international collaborations: please, refer to part 3.

2.5. Outputs and Results

Please refer to point 2.1.1. for the number of individuals at each stage of the study.

Published results and ongoing publications; twelve original articles have been published in peer-reviewed journals from October, 2006, through February, 2008.[1-12] Nine additional papers have been submitted, and are currently under review or revision.[13-21] These 21 papers represent the work of the present grant during a period of two years and will be summarized under following headings.

2.5.1. Outdoor air pollution and health

The effect of living near main streets on respiratory symptoms in adults was studied with the SAPALDIA 1 and 2 data. The length of main street segments within 200 m of the home, and the distance from home to the closest main street were used as an approximation of individual exposure to traffic pollution. It was found that the risk of attacks of breathlessness, regular phlegm and wheeze were increased for people living near busy streets. This was the first paper documenting adverse respiratory effects of traffic-generated air pollution in a general adult population.[2]

Based on exposure estimates from our dispersion model,[9] it was possible to assign home outdoor exposure to PM_{10} for every SAPALDIA subject at both the 1991 and the 2002 surveys and in the intervening years. We found significant negative associations between the decrease in PM10 and the rate of decline in FEV1, FEV1/FVC%, and FEF25-75. For example, a decline of 10 $\mu g/m^3$ in PM_{10} over an 11-year period was associated with a reduction in the annual rate of decline in FEV1 by 9 % and in FEF25-75 by 16%. Thus, reducing exposure to airborne particulates appeared to attenuate age-related decline in lung function in adults from the general population.[10] Our paper provided the first evidence that air pollutants can accelerate a decline in lung function during adult life. Our findings further support a causal role of exposure to air pollution in respiratory health. Relatively small reductions in exposure to PM_{10} have measurable benefits for lung function, suggesting that a decline in air pollution, even from low levels, may have positive consequences for public health.

We have submitted two additional papers on air pollution health effects. First, we could show that the decline in individual exposure to PM_{10} was also associated with both a reduced incidence and reduced persistence of respiratory symptoms on follow-up.[21] In another paper, we examined the effect of exposure to traffic related NO_2 after our group had developed an innovative hybrid model [18] to estimate individual exposure to this gaseous pollutant. In this paper we show that higher levels of exposure to NO2 during the year preceding the 24-h electrocardiogram (ECG) recording in 2002 were

associated with reduced heart rate variability in adults with cardiovascular disease and in women . These are the first results supporting the hypothesis that long-term exposure to NO_2, a traffic-related pollutant, is associated with cardiac autonomic dysfunction, a prognostic marker for cardio-vascular diseases. [19] In fact, all previously published results relating heart rate variability to air pollution were concerned with short term effects. The reason for the greater vulnerability of women in our study is not clear and will need further investigations.

2.5.2. Exposure assessment to outdoor air pollutants

Exposure estimates from dispersion model: We evaluated total and traffic-specific PM_{10}, $PM_{2.5}$, NO_2, and NO_x concentrations predicted by Gaussian dispersion models against fixed-site measurements at different locations including traffic impacted, urban background, and Alpine settings between and across 8 SAPALDIA areas. The model predictions were then used to estimate individual subjects' historical and cumulative exposures with a temporal trend model. The dispersion model predicted well total PM_{10}, NO_x, and NO_2 and traffic-specific pollution at background sites. However, the model under-predicted traffic-NO_x and NO_2 at traffic sites and needs refinement to reflect local conditions. By contrast, the dispersion model predictions for PM_{10} appeared suitable for examining individual exposures and health effects within- and between-cities.[9]

Exposure estimates from innovative hybrid models: In light of the failure of the dispersion model for accurate predictions of NO_2 within cities, we developed innovative models utilizing home outdoor NO_2 measurements, geographic parameters, and the dispersion model estimates. Passive NO_2 measurements were taken outside of up to 100 residences per area in 1993 and 2003. Our results indicated that models should be constructed for individual areas and years, and use the dispersion estimates as the urban background, geographic parameters to enhance local characteristics, and temporal and meteorological variables for local dynamics. Such model predictions provide a powerful tool for assessing health effects from long-term exposure to air pollution in a large cohort.[18]

2.5.3. Indoor air pollution, second hand smoke

SAPALDIA has been pioneering research on the effects of second-hand smoke (or passive smoking) since 1994 (P. Leuenberger et al, Am J Respir Crit Care Med, 150:1221-8). During the present grant our group has produced three additional papers in major international journals.[3,6,8] Gerbase et al[3] have shown that the effect of second hand smoke is particularly important in persons with bronchial hyper-responsiveness which represent about 16% of the general population (e.g. relative risk of 7.89 for chronic bronchitis with continued exposure to second hand smoke over the eleven year follow-up period). Bridevaux et al[8] have shown that second hand smoke impairs health related quality of life in exposed subjects with a dose-dependent relationship. Women appear to be more vulnerable than men, and more so when exposure occurs at home. Finally, Felber Dietrich at al[6] showed that subjects exposed to second hand smoke for more than 2h/day had lower heart rate variability which suggests increased cardiac risk through disturbances in the autonomic nervous system.

2.5.4. Gene-environment interaction

Supported by the present grant, several analyses involving data from our biobank and lab centre in Zurich showed that variations in genes of the glutathione S-transferase super family are associated with age-related lung function decline in adults,[4] modify the likelihood of progression from silent BHR to incident asthma in adults,[11] and interact with passive smoking in its impact on heart rate variability.[20] Also, in the context of a thesis in human biology at the University of Zürich, we have identified a rare IL-6 variant to be strongly associated with several of the respiratory and allergic outcomes as well as with ST-depression on ECG (Mächler 2007, thesis). Finally, we have conducted a pooled analysis of DNA samples from SAPALDIA and ECRHS, which resulted in the largest collaborative effort addressing the association between TNFA and LTA genetic variants with asthma. Based on over 11'000 subjects and by including a meta-analysis of all published studies we confirmed the association between genetic variation in TNFA and asthma-related phenotypes.[16] Pooled analyses for a second paper involving the two cohorts to investigate the interaction between obesity and TNFA in asthma are ongoing.

In a PhD thesis on genetic determinants of COPD (Dr. I. Curjuric, supervised by N.Probst-Hensch, in prep.) we found that polymorphisms in hemeoxygenase-1 are related to the age-related decline in lung function. In addition, variation in the HMOX1 and GSTP1genes modify the association between outdoor air pollution exposure to PM_{10} and age-related lung function decline that we have reported.[10] Finally, in a separate analysis, we also found very strong and novel interactions with cell cycle control gene variants (Imboden et al, in prep.).

2.5.5. Asthma and atopy

A collaborative work with ECRHS has been published that confirmed the association of asthma and obesity, particularly in women.[1] Another collaborative work with the Unit for experimental Immunotherapy at the University Hospital in Zurich resulted in a publication supporting the hypothesis that the first few months of life constitute a sensitive period during which inhalation exposure may predispose to the subsequent development of atopic respiratory diseases.[5] A new collaboration with the Horten Centre for patient-oriented research at the University Hospital in Zurich addressed the question of disease-specific versus generic health-related quality of life instruments for asthma in the general population, and has just been accepted for publication.[12] Finally, a nested project in collaboration with the Center for Research and Environmental Epidemiology in Barcelona is addressing the question of new onset of adult asthma and traffic-related air pollution (Kuenzli et al, in prep.)

2.5.6. COPD

Little is known on the long term outcomes of individuals with mild COPD. At SAPALDIA 1 criteria for COPD were met by 610 (9.1%) participants from whom 519 (85.1%) had stage 1 COPD according to the GOLD classification (Global Initiative for Obstructive Lung Diseases). After eleven years, individuals with symptomatic GOLD 1 COPD (n=224) had faster FEV_1 decline, increased respiratory care utilization and lower quality of life compared to asymptomatic subjects with normal lung function. In contrast, asymptomatic GOLD 1 COPD subjects (n=295) did not differ from the reference group. Thus, respiratory symptoms are of major importance for predicting clinical outcomes in COPD subjects. These results have major relevance for public health because studies that are based on spirometry only may misestimate the prevalence of clinically relevant COPD.[17] Two additional manuscripts on prevalence and incidence of COPD in the SAPALDIA cohort are in preparation (Probst-Hensch et al). This work will provide the first data for Switzerland on the epidemiology of this important disease which is a major cause of morbidity and early mortality worldwide.

With data from over 6000 subjects, the SAPALDIA cohort has one of the largest data bases worldwide for serum levels of both alpha-1 antitrypsin (AAT) and high-sensitive C-reactive protein (CRP) . A positive association between AAT and lung function was found to be restricted to heavy smoking men and postmenopausal women, after adjustment for CRP.[14] In collaboration with the Italian AAT registry (Prof. M. Luisetti), SAPALDIA participants with an AAT level below a threshold associated with a high likelihood of genetic AAT deficiency were genotyped for SERPINA1 variants, i.e. the gene coding for AAT.[15] This description of genotypes with circulating AAT is the first, comprehensive population-based characterization of severe and intermediate AAT deficiencies.

2.5.7. Risk factors of cardio-respiratory health

We investigated whether regular exercise was protective against reduced heart rate variability (HRV), and whether adverse effects of obesity and weight gain on HRV were modified by regular exercise. Compared to sedentary obese subjects, HRV was 14% higher in sedentary normal weight subjects; 19% higher in normal weight subjects exercising regularly; and 19% higher in obese subjects exercising regularly.[13] The Ph.D. student (Felber-Dietrich) who presented these results at the World Congress of Cardiology 2006 in Barcelona received the Young Investigators Award from the European Society of Cardiology.

We also examined potential associations between dietary habits, physical activity and HRV (abstract to the Eur. Soc. of Cardiol. 2007), and found that subjects regularly eating fruit had higher HRV, an effect that is adding to the beneficial effect of regular exercise.

COPD is an independent risk factor for cardio-vascular disease and mortality, and systemic inflammation is believed to mediate this association. We found that high-sensitivity CRP was elevated both in association with weight gain and fast FEV_1 decline. Interaction between weight change and fast FEV_1 decline was significant in women but not in men, resulting in greater systemic inflammation. These results may shed light on the observed gender differences in severity of COPD. (Bridevaux et al, in prep.).

2.5.8. Other work on gender research

Variability of reproductive history in the SAPALDIA Swiss cohort is the topic of a new article that has been just published by our group.[7] This article also addresses determinants of menopausal age. Subsequently, Dr. Dratva and Dr. Zemp were invited to include the respective data of the ECRHS into their analyses (Dratva et al, in prep.).

2.6. Discussion and Conclusion

The recent publications by the SAPALDIA team have addressed the key questions of the project: i) the impact of air pollution on respiratory and cardio-vascular health in a longitudinal perspective; ii) the role of genetic factors in modifying health effects from the environment, and iii) the complex interactions between respiratory and cardiovascular health. Further studies and refinements are necessary to address many unresolved issues. These require extensive collaborations, particularly in the fields of exposure assessment and genetic associations. Moreover, in this ageing cohort, a third survey is now essential: the increasing prevalence of cardio-respiratory morbidity and a third measurement of pulmonary function tests will provide important additional information on health outcomes.

2.7. List of publications (in chronological order from August, 2006 until February, 2008).

1. Chinn S, S. H. Downs, J. M. Anto, M. W. Gerbase, B. Leynaert, R. de Marco, C. Janson, D. Jarvis, N. Künzli, J. Sunyer, C. Svanes, E. Zemp, U. Ackermann-Liebrich, P. Burney on behalf of the ECRHS and SAPALDIA teams. Incidence of asthma and net change in symptoms in relation to changes in obesity. Eur Respir J, 2006; 28: 763 - 771.

2. Bayer-Oglesby L, Schindler C, Hazenkamp-von Arx ME, Braun-Fahrlander C, Keidel D, Rapp R, Kunzli N, Braendli O, Burdet L, Sally Liu LJ, Leuenberger P, Ackermann-Liebrich U. Living near Main Streets and Respiratory Symptoms in Adults. Am J Epidemiol. 2006; 164: 1190-1198.

3. Gerbase MW, Schindler C, Zellweger JP, Künzli N, Downs SH, Brändli O, Schwartz J, Frey M, Burdet L, Rochat T, Ackermann-Liebrich U, Leuenberger P. Respiratory effects of environmental tobacco exposure are enhanced by bronchial hyperreactivity. Am J Respir Crit Care Med. 2006; 174: 1125-31.

4. Imboden M, Downs SH, Senn O, Matyas G, Brändli O, Russi EW, Schindler C, Ackermann-Liebrich U, Berger W, Probst-Hensch NM. Glutathione S-transferase genotypes modify lung function decline in the general population: SAPALDIA cohort study. Respir Res. 2007; 8: 2-.

5. Graf N, Johansen P, Schindler C, Wuthrich B, Ackermann-Liebrich U, Gassner M, Kundig TM, Senti G. Analysis of the Relationship between Pollinosis and Date of Birth in Switzerland. Int Arch Allergy Immunol. 2007; 143: 269-75.

6. Felber Dietrich D, Schwartz J, Schindler C, Gaspoz JM, Barthelemy JC, Tschopp JM, Roche F, Von Eckardstein A, Brändli O, Leuenberger P, Gold DR, Ackermann-iebrich U, SAPALDIA Team (2007). Effect of passive smoking on heart rate ariability, heart rate and blood pressure: an observational study. Int J Epidemiology 2007; 36: 834-840.

7. Dratva J, Zemp E, Staedele P, Schindler C, Constanza M, Gerbase MW, Probst-Hensch NM, Rochat T, Ackermann-Liebrich U. Variability of reproductive history across the Swiss SAPALDIA cohort - Pattern and main eterminants. Ann Hum Biol 2007, 34, 437-453.

8. Bridevaux PO, Cornuz J, Gaspoz JM, Burnand B, Ackermann-Liebrich U, Schindler C, Leuenberger P, Rochat T, Gerbase MW. Does environmental tobacco smoke affect health related quality of life? Results from the SAPALDIA study. Arch Intern Med 2007, 167, 2516-2523.

9. Liu LJS, Curjuric I, Keidel D, Heldstab J, Künzli N, Bayer-Oglesby L, Ackermann-Liebrich U, Schindler C, SAPALDIA Team. Characterization of Source-Specific Air Pollution Exposure for a Large Population-Based Swiss Cohort (SAPALDIA). Environ Health Perspect. 2007, 115, 11, 1638-1645.

10. Downs S, Schindler C, Liu LJS, Keidel D, Bayer-Oglesby L, Brutsche M, Gerbase ME, Keller R, Künzli N, Leuenberger P, Probst-Hensch N, Tschopp JM, Zellweger JP, Rochat T, Schwartz J, Ackermann-Liebrich U. Reduction in PM10 attenuates age-related lung function decline in adults. N Engl J Med 2007, 2338-2347.

11. Imboden M, Rochat T, Brutsche MH, Schindler C, Downs SH, Gerbase MW, Berger W, Probst-Hensch NM. Glutathione-S transferase genotype increases risk of progression from bronchial hyperresponsiveness to asthma in adults. Thorax. 2007 Dec 5 (Epub ahead of print).

12. Puhan MA, Gaspoz JM, Bridevaux PO, Schindler C, Ackermann-Liebrich U, Rochat T, Gerbase MW. Comparing a disease-specific and a generic health-related quality of life instrument in subjects with asthma from the general population. Health Qual Life Outcomes 2008, in press.

Submitted articles :

13. Felber Dietrich D, Ackermann-Liebrich U, Schindler C, Barthelemy JC, Brändli O, Gold DR, Knöpfli B, Probst-Hensch N, Roche F, Tschopp JM, von Eckardstein A, Gaspoz JM.. Effect of physical activity on heart rate variability in normal weight, overweight and obese subjects: results from the SAPALDIA study. Submitted, Feb 2008 (European Journal of Applied Physiology).

14. Senn O. Russi EW, Schindler C, Imboden M, von Eckardstein A, Brändli O, Zemp E, Ackermann-Liebrich U, Berger W, Rochat T, Luisetti M, Probst-Hensch NM. Circulating alpha-1-antitrypsin in the general population: determinants and association with lung function. Submitted, Feb 2008 (Respir Res).

15. Zorzetto M, Russi EW, Senn O, Imboden M, Ferrarrotti I, Tinelli C, Campo I, Ottaviani S, Scabini R, Berger W, Brändli O, Rochat T, Luisetti M, Probst-Hensch NM.. SerpinA1 gene variants in individuals from the general population with reduced alpha-1-antitrypsin serum level. Submitted, to Clin Chem, in revised from Feb 2008.

16. Castro-Giner F, Kogevinas M, Mächler M, decide R, Van Steen K, Imboden M, Schindler C, Berger W, Gonzalez JR, Franlin KA, Janson C, Jarvis D, Omenaas E, Burney P, Rochat T, Estivill X, Anto JM, Wjst M, Probst-Hensch NM.. *TNFA-308* in two International population-based cohorts shows increased risk for asthma. Submitted to Eur Respir J, in revised form Feb 2008.

17. Bridevaux PO, Gerbase MW, Probst-Hensch NM, Schindler C, Gaspoz JM, Rochat T.. GOLD stage 1 COPD: long term lung function decline, utilization of care and quality of life. Submitted to Thorax, in revised form Mar 2008.

18. Liu LJS, Keidel D, Gemperli A, Ineichen A, Hazenkamp M, Bayer L, Künzli N, Ackermann-Liebrich U, Straehl P, Schwartz J, Schindler C. long-term exposure models for traffic related No2 across geographically diverse areas over separate years. Submitted, Feb 2008 (Am J Epidemiol).

19. Felber Dietrich D, Gemperli A, Gaspoz JM, Schindler C, Liu LJS, Gold DR, Schwartz J, Rochat T, Barthelemy JC, Pons M, Roche F, Probst-Hensch NM, Bridevaux PO, Gerbase MW, Neu U, Ackermann-Liebrich U.. Differenecs in heart rate variability associated with long-term exposure to NO2. Submitted, Feb 2008 (Environ Health Perspect).

20. Probst-Hensch NM, Imboden M, Felber Dietrcih D, Barthelemy, JC, Ackermann-Liebrich U, Berger W, Gaspoz JM, Schwartz J.. Glutathione S-transferase polymorphisms, passive smoking, obesity and heart rate variability in adult non smokers. Submitted, Feb 2008 (Env Health Perspect).

21. Schindler C , Keidel D, Gerbase MW, Zemp E, Bettschart R, Brändli O, Brutsche MH, Burdet L, Karrer W, Knöpfli B, Pons M, Schwartz J, Rapp R, Liu LJS, Bayer-Oglesby L, Künzli N, Ackermann-Liebrich U, Rochat T. Improvements in PM10-exposure and reduced rates of respiratory symptoms in a cohort of Swiss adults (SAPALDIA-study). Submitted, Mar 2008 (Am J Respir Crit Care Med)

3. Update of scientific plan and future perspective (max 4 pages)

3.1. Ongoing multinational collaborations in the field of exposure assessment

European Study of Cohorts for Air Pollution Effects (ESCAPE). One of the issues emerging from our exposure assessment efforts regards the lack of specific traffic markers in SAPALDIA for assessing traffic-specific exposure. Not all predictors in our hybrid models for NO_2 are traffic related. The Swiss emission inventory indicated that on average 47 percent of NOx came from direct traffic emissions (range: 20 percent in Wald to 63 percent in Lugano). The association between our hybrid model predictions for NO_2 and traffic exhaust is still confounded by other sources. To resolve this issue as well as health effect issues regarding long-term exposure to source-specific pollution, we are currently participating in a European-wide Study (ESCAPE), which will quantify effects of long-term exposure to outdoor air pollution on human health across 30 cohorts in 44 cities. Effects to be examined in ESCAPE include pregnancy outcomes and developmental effects in birth cohorts, respiratory disease outcomes in adults, cardiovascular disease outcomes in adults, and cancer incidences and cause-specific mortality. SAPALDIA participates in work packages involving three of the health outcomes. SAPALDIA (Liu) also leads the central-Europe environmental exposure center in charge of monitoring and modeling of particulate matter, using markers such as soot or a combination of specific chemicals for diesel exhaust as indications of traffic exposure. Airborne particulate matter will be characterized as inhalable (PM_{10}) and respirable ($PM_{2.5}$) particles as well as 'soot' and elemental composition. Both NO and NO_2 will be measured in view of changing NO/NO_2 ratios in primary traffic emissions which may affect compliance with the European legislation with respect to NO_2 coming into force in 2010.Three of the SAPALDIA sites (Basel, Geneva, and Lugano) will be part of the monitoring/modeling efforts. Our collaboration with ESCAPE will result in a unified methodology for assessing within-city or within-area contrasts in long-term average concentrations of airborne particulate matter and nitrogen oxides across participating cohorts.

Air Pollution and Risks for Life Quality in a Changing Alpine Climate (CLAIR-ALPS). SAPALDIA (J.-L. S. Liu) is the lead partner of a workpackage on "assessment of air pollution impacts on health and life quality" in an Alpine Space Programme proposal on CLAIR-ALPS. This proposal involves a multi-national and multi-disciplinary team and investigates air quality issues in the Alpine environment, which is particularly vulnerable and increasingly impacted by anthropogenic sources (e.g. tourism, commercial traffic flows, biomass burning for domestic heating) as well as by the changing climate. An additional feature of the complex topography in the alpine space results in most human activities being concentrated in the valley floor. This poses specific problems with respect to air quality and quality of life, since the communities are forced to live next to large emission sources. The eight SAPALDIA study areas represent diverse communities (urban, rural, mountainous, and receptor sites) in the alpine space facing these challenges. We will be leading and coordinating the efforts on community exposure and health assessment for air pollution and climate change cross cities in Switzerland, Austria, Northern Italy, Southeastern France (Grenoble), and Southern Germany.

High Performance Computing **(HPC)-Europa 2008++.** As part of the cohort maintenance effort to refine dispersion models for ambient air pollutants, the SAPALDIA environmental exposure center (J.-L. S. Liu) is also collaborating with a group of meteorologists and modelers in Basel and the pan-European Research Infrastructure on HPC-Europa 2008++ in Barcelona. This effort focuses on advancing modelling of air pollution through comprehensive modelling of meteorology at a fine spatial scale (1 km or less). We aim to model long-term air pollution for the entire Switzerland with a dispersion model and the state-of-the-art Weather Research and Forecasting model (WRF), coupled with the associated chemistry extension (WRFchem). This concerted effort involves the first air pollution model on a long-term and large regional scale (i.e., the entire Switzerland). Such modelling effort with a fine spatial resolution will provide important information on air pollution evolution due to changes in sources and climate across Switzerland as well as within regions, (e.g., mountainous Alpine areas and urban areas). In addition, such spatially resolved data will provide a break-through in

the field of air pollution epidemiology for exposure and health effect assessment of pollutants originated from sources such as traffic, wood burning, industrial activities, and others.

3.2. Ongoing national and multinational collaborations in the field of gene association studies

SAPALDIA (N.Probst-Hensch) is a partner in two international consortia conducting genomewide scans for asthma and lung function, respectively. In the context of the 6th framework programme project, GABRIEL (www.gabriel-fp6.org) unifies a large set of international study populations on asthma. SAPALDIA will provide asthma case and control DNA to be included in a genome-wide scan for asthma. The study will provide SAPALDIA with over 500'000 SNPs including copy number variants from the according Illumina Chip on all asthma cases and a random sample of roughly 1000 controls. Negotiations about collaborations with additional studies, including ECRHS, for detailed assessment of gene-environment interactions based on novel meta-analytic approaches to the genome-wide scan results across studies are ongoing.

In addition the whole SAPALDIA cohort will be genotyped for a set of selected genotypes resulting from the genomewide scan as well as a set of candidate SNPs. In the context of KORA Gen, the group of N.Probst-Hensch is taking the lead on a genome-wide scan for lung function in the KORA Gen population. KORA is a population-based adult cohort from Bavaria, Germany, which was attending repeated health assessments at various time points. It is coordinated by the Helmholtz Stiftung in Munich (Prof. E. Wichmann) and provides spirometry results on the lung function of roughly 600, well characterized subjects . The analysis of the association of 500'000 SNPs from the Affimetrix Chip with FEV1 and FVC is finalized. Genotyping for validation of strong SNP/lung function association in SAPALDIA is ongoing and expected to be finalized by mid-April, 2008. As the KORA Gen consortium includes genome-wide scans for various phenotypes, SAPALDIA has agreed to provide samples for replication of findings related to HDL as an outcome (F. Kronenberg, Innsbruck).

SAPALDIA and ECRHS are collaborating in analyses on the relevance of copy number variants to asthma and atopy (X. Estiville/M. Kogevinas/R. de Cid) and a genomewide scan based on pooled DNA samples.

SAPALDIA (N.Probst) is a co-applicant in an NIH-proposal to identify novel genes potentially responsible for the modulation of air pollution on cardiovascular disease (PI: Prof. A. Peters, Helmholtz-Stiftung, München).

SAPALDIA is supporting work conducted by the group of M. Hersberger at the University of Zürich who is studying the relevance of genetic variants in the lipoxygenase pathway to asthma (Hersberger et al.).

3.3. Ongoing multinational collaboration in occupational exposure

The study of specific occupational exposures requires large samples in order to reach sufficient numbers of exposed subjects. A joint project pooling the data from ECRHS and SAPALDIA investigates respiratory health risks associated with occupational exposure to specific cleaning substances for which the numbers of exposed persons are of the order of a few percent of the population (presented at the Eur Respir Society congress, Sept 2007). A first manuscript will soon be finished and analyses will then continue with a focus on gene-environment interactions.

3.4. Design of SAPALDIA 3 (update of the plan submitted in 2005)

Background to the design of SAPALDIA 3: Systemic inflammation is a hallmark of chronic exposure to ambient pollutants which consist in a mixture of several strong oxidants resulting in oxidative stress and both local and systemic inflammatory responses. Much remains to be investigated on the pollution-related link between pulmonary responses and cardiovascular pathologies. SAPALDIA 3 offers the opportunity to expand the research focus more explicitly on 'systemic inflammatory syndromes' and related chronic disease pathologies, in particular COPD, asthma and atherosclerosis.

This third examination is planned to start in the second semester of 2009, i.e. 19 years after the first assessment and 8 years after the second assessment. As the population ages (37-79 in 2009), more frequent examinations are needed in order to obtain information on the development of age-related diseases. The preparation phase for the third examination will be initiated in the fall of 2008 and will include: re-evaluating of the questionnaires, testing new spirometers and piloting all the health examinations, recruiting and training fieldworkers (medical and technical) at the local centres in the 4 months preceding the start of the study. Local centers have to be equipped and prepared for the examination period. All former participants (in SAPALDIA 1 and 2) will be invited to the local centres for a third health assessment. Participants who have moved will be invited to the nearest SAPALDIA centre and travelling costs will be reimbursed to those who have moved out of a SAPALDIA region (10% of participants in 2002).

The health examinations will take place in the same centers as in SAPALDIA1 and SAPALDIA2 (i.e., in Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, Wald) during one year, i.e., until the summer of 2010. The examination will consist of the main elements of SAPALDIA 1 and 2 including:

1. An extensive computer-based interview based on the questionnaires of SAPALDIA 2 for current symptoms and diseases (also including questions on health and disease-related problems since 2002, on lifestyle, occupational and other exposures and on physical activity).

2. Measurements of weight, height and waist and hip circumference in order to follow the development of weight gain and obesity.

3. Spirometry conducted according to the methodology in SAPALDIA 1 and 2 using the same rigorous quality controls as described in the cohort (Künzli et al, Eur Respir J 1995, 8, 371-6). New spirometers will be purchased and tested; we now plan to use Biomedin equipment as recommended by ECRHS. A reversibility test will be performed as well as measurement of the inspiratory capacity for assessment of COPD. We do not plan to include a third methacholine bronchochallenge as part of the general examination of the cohort. NO-exhalation test and measurements of components of breath condensate may be planned as a separate project according to the rapid progress in these technologies.

4. Endexpiratory CO concentration using EC50 Micro-Smokerlyser (Bedfont Rochester UK) and cotinine (the major metabolite of nicotine) in saliva to validate active and passive smoking status.

5. Blood samples: The specific aim for the additional collection of biological material at SAPALDIA 3 is the collection of additional plasma and serum samples for the longitudinal measurement of relevant blood markers already investigated in SAPALDIA 2 (glucose, hs-CRP; HDL-cholesterol; triglycerides; uric acid; creatinine; alpha-1 antitrypsin).. In addition, we will consider heparin blood with DMSO for EBV-transformed cell lines for unlimited DNA-availability and biological samples suitable for gene expression and proteomic studies.

6. Blood Pressure will be measured as in 2002 with an automatic OMRON 705 CP (Tokyo, Japan) after a quiet rest of at least 10 minutes.

7. All participants who had an ECG in 2002 (1'707) and a random sample of those aged 50-57 at the third assessment will be offered a 24 hour Holter ECG. The methodology will be the same as that in SAPALDIA 2 and the ECG s will be analyzed in St. Etienne at the same laboratory as in 2002 by Prof. Barthélémy and his team. In particular, present findings of cross-sectional associations between average ambient levels of NO2 and decreased heart rate variability raise important questions regarding the reversibility or chronicity of such effects.

8. A telephone interview will be conducted if participants are unable or unwilling to attend the examination centre. However, every effort will be made in order to motivate people to participate in the examination, e.g., by reimbursing travel costs.

9. An important goal of SAPALDIA3 will be to detect early signs of cardio-vascular and respiratory morbidity in a sufficient number of the ageing population. Measurement of carotid intima-media thickness (IMT) by ultrasound allows for detection of atherosclerosis and arterial wall rigidity. It has the advantage of reflecting long term effects on the vascular system, while heart rate variability may be affected by short term exposure. It has already been used in large population studies, and contacts have been made with a laboratory at the Amsterdam Medical Centre that has considerable experience for this measurement in studies with large numbers of participants. Other tools that will be evaluated for applicability during the preparation year of SAPALDIA3 (i.e. 2008) include Vascular Pulse Velocity (as a cheaper alternative to carotid IMT), exhaled NO (e.g. as a nested study), light systems of polygraph recording for sleep-related respiratory disorders, and simple cognitive tests (e.g. mini-mental status or others) for those aged >70 on the hypothesis that ultra fine particles may contribute to brain function decline. We will also consider gene expression patterns in the blood of sub-samples of participants, and detailed assessment of nutrient intake by food frequency questionnaires and 24-hr-recalls.

10. Comprehensive exposure monitoring and modeling, leveraging ongoing and proposed multi-national collaborations for outdoor, indoor, and personal environments and to take into account infiltration efficiency and differences in personal time-activities. Additional pollutants to be monitored will include ultra-fine particulate matter (UPM), components of PM for source apportionment, and NOx.

The organization of SAPALDIA will require a responsible physician at every centre for one year plus three months of preparatory work and a spirometry-technician with laboratory skills for 18 months at each centre (including 4 months for preparation and 2 months for closing down of the center). For the whole logistic and data transfer and the installation of the electronic tools, our computer specialists in Basel and Geneva providing the informatics support for the project will ensure that the data can be sent on a daily basis from the local centres to the health data center in Basel and to the address data center in Geneva. This will enable efficient data cleaning and timely feedback to the local fieldworkers. As a consequence, data quality will be further improved and analyses can be started earlier. We therefore expect to be able to publish first results in 2011. An additional data manager will be required in data centre in Basel. Blood collection and the set-up of the SAPALDIA 3-biobank will be planned and coordinated by the molecular biologist and the genetic lab technician.

Based on our experiences with SAPALDIA 2, we anticipate re-examining about 6'000 SAPALDIA participants and to obtain health data on about 7'500 participants.