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WPL-1 RATIONALE OF THE PRECAUTIONARY PRINCIPLE: THE FRENCH EXPERIENCE

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Meeting society's expectations without avoiding new concerns and without falling into manipulation, pessimism or fantasy. To seek this subtle balance, one should first recognize that, with regards environmental health, any concern deserves at least an echo, if possible an answer, and failing this, at least an open door towards research.

The « Environmental Health » group from the French Parliament, which I have the honour to chair, has, during its various studies, brought forward the fact that questions related to environmental health are not longer insignificant. Public queries, and sometimes concerns, are on the increase. Chemical substances, air quality, food... the subject is multiform, has various facets.

We have therefore organised in 2003 a conference on noise, then on the impact of chemical substances on health, and in 2005 on electromagnetic fields. The same conclusions apply to each event: answers must be provided.

This is one of the great challenges which the Environment Bill, now included in the French Constitution, intends to address. The first article of the Environment Bill states that:

"Everyone has the right to live in a stable and health friendly environment".

In particular, in article 5, the Environment Bill provides a definition of the precautionary principle:

"When it is recognised that some prejudice, though such recognition is uncertain owing to the current scientific knowledge, may have a serious and irreversible impact on the environment, public authorities ensure, through the enforcement of the precautionary principle and within their field of competence, the implementation of risk assessment procedures and provisional and proportionate measures in order to prevent such prejudice".

These clauses therefore attempt to provide an answer to everyone – anxious citizens, motivated or doubtful researchers and undecided decision-makers – by proposing a procedure, a protocol and maybe simply "good practice" to face the challenges of scientific uncertainty in environmental issues. We have been looking for such answers for over fifty years. Ecology, particularly environmental health, issues open wide access to a new world. This is now the dawn of the era of responsibility. And we cannot backtrack.

What are the first lessons? My experience is twofold, both as the Reporter of the constitutional Environmental Bill and as the Chair of the « Environmental Health » group from the French Parliament; it first points towards better coordination, better communication between the various actors. Competences are at present too widely spread, hence diluted. Let us take an example. In a field such as the impact of chemical substances, roughly twenty organisations are acknowledged as competent in France. How can we cross data, interpretations, recommendations? This is one of the great political challenges.

WPL-2 ENVIRONMENTAL GENOMICS: AN OPPORTUNITY FOR THE NIEHS

As I continue to consider new research opportunities for the NIEHS, my desire to support research in environmental genomics grows. While the accomplishments and available tools in genetics and genomics certainly enhance my enthusiasm for this field of research, my attraction to environmental genomics stems from my belief that environmental exposures can be used to understand the role of transcriptional regulation and genetic variation in the development and progression of common, yet complex human diseases.

A growing body of research helps to illustrate the opportunities and challenges that lie before us. The influence of environmental exposures on transcriptional regulation of genes is clearly highlighted by the field of epigenetics. Michael Skinner at Washington State University and colleagues recently demonstrated the potential transgenerational adverse effects of intrauterine exposure to endocrine disrupting pesticides on male fertility (Anway et al. 2005). Findings from Randy Jirtle's laboratory at Duke University indicate that exposure through maternal diet to common methylating agents found in vegetables and vitamin supplements can have profound effects on gene expression in offspring that continue to be inherited in subsequent generations (Waterland and Jirtle 2003). Moreover, since monozygotic twins diverge in the concordance of methylation as a function of age (Fraga et al. 2005), it is abundantly clear that methylation is a dynamic process. These findings underscore the role that intrauterine exposures could potentially have on common complex diseases that involve developmentally vulnerable organ systems. Such research also indicates that environmental exposures may serve as biological clues to understanding the regulation of gene expression and the role that transcriptional regulation may have on the risk of developing disease, as well as point to novel therapeutic interventions.

Environmental exposures can also be used to simplify complex biological processes to both discover unique biological mechanisms and to narrow the pathophysiologic phenotype of complex human diseases. For instance, the discovery of the aryl hydrocarbon receptor (AHR) occurred as a direct result of the known toxicity of dioxin and polycyclic aromatic hydrocarbons. Not only did this discovery demonstrate the biological role of the AHR in mediating the toxicity to these agents, but it revealed the role of AHR in homeostatic and basic pathophysiologic processes. Most importantly, however, the identification of the AHR led to the ultimate discovery of the PAS (PER-ARNT-SIMS) superfamily of receptors that mediate response to various forms of environmental stress such as hypoxemia and circadian rhythm, and control basic physiologic activities such as vascular development, learning, and neurogenesis (Kewley et al. 2004; Nebert et al. 2004). Likewise, understanding of environmental exposures can simplify complex disease processes by narrowing the pathophysiologic phenotype to elucidate the genetics and biology that underlie a particular condition. For example, diseases such as asthma arise from dozens of etiologic agents. Since asthma caused, or exacerbated, by dust mites, endotoxin, or ozone involves different genes and different biological mechanisms, the disease can be better studied by focusing the investigation on a specific etiologic type of asthma.

Given that an extensive number of animal genomes have been sequenced and have demonstrated the evolutionary conservation of biology and genetic structure, comparative genomics will be an important tool for identifying the genes that control response to specific environmental agents, which in turn will accelerate our discoveries in environmental health science. For instance, the discovery of the importance of the toll-like receptors in innate immunity in mammals occurred as a direct result of the observation that a defective receptor in flies caused them to be much more susceptible to *Aspergillus fumigatus* (Lemaître et al. 1996; Medzhitov et al. 1997). The ease with which we can observe and apply knowledge across model systems must be exploited so that we can efficiently understand the biological and clinical importance of environmentally responsive genes.

To facilitate progress in environmental genomics, we need to train young investigators in the discipline, and support scientific programs that focus on biological and clinical problems that can most directly be solved by employing these novel conceptual and methodological approaches. However, to truly have an impact on human health, we need to extend these approaches to understanding chronic complex human diseases including cardiac disease, cancer, diabetes, chronic lung disease, and cerebrovascular disease. While these diseases are known to account for substantial morbidity and mortality worldwide, avoidable environmental exposures and reversible behaviors play a critical role in their development (Willett 2002). A clear challenge to the field of environmental health sciences will be to make the best use of environmental genomics to inform our understanding of the interaction between environmental exposures and genes in the development and progression of human diseases, and ultimately to translate this knowledge into effective prevention, intervention, and treatment strategies.ⁱⁱ

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ⁱ Since used again below.

ⁱⁱ Expand to global?

ⁱⁱⁱ Was trying to tie in and finish off the idea of the preceding sentence...

WS1 DIOXIN EXPOSURE AND HUMAN HEALTH 30 YEARS AFTER THE SEVESO, ITALY ACCIDENT

Pier Alberto Bertazzi

WS1-01 THE SEVESO ACCIDENT. A PROTOTYPE OF ENVIRONMENTAL EPIDEMIOLOGY CHALLENGE.

Pier Alberto Bertazzi, Department of Occupational Health, University of Milan and Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena, Milan, Italy

The accident that occurred near the town of Seveso, Italy in 1976, caused exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD or dioxin) in a large population. The sudden release from a trichlorophenol manufacturing plant of a cloud of chemicals gave immediate signs of hazard: vegetation, birds, courtyard animals and people were seriously affected; children were admitted to the local community hospitals for skin lesions. The presence of TCDD as the main component of the toxic cloud was made known 10 days after the accident. Fear for the health of local residents was justified by the known high toxicity of TCDD in animals and its ability to cause cancer in experimental conditions. Little was known, instead, at that time, about its effects on human beings, especially after environmental exposure. In addition, application of modern epidemiological methods to environmental issues was just taking its first steps. In the emergency situation following the accident, health authorities and researchers were confronted with three main problems: ascertaining the nature and characteristics of the exposure, the extent of contamination, and the number of people involved; managing the risk with preventive measures for people and the environment; planning and conducting health surveillance programs. The examination of the early and mid-term effects was anything but simple in the complex post-accident situation. The hectic conditions in the area jeopardized the validity of health investigations. Selective participation, lack of reference data, limited standardization of methods and performances were common problems; this is why many studies yielded inconclusive results. Long term studies were designed later and were less affected by those constraints. Other type of inherent limitations affected these studies as, for example, the limited number of individual exposure measurements, the short latency period for certain events and the small size of the highly exposed population. The disaster experience with its burden of psychosocial stressors exposure probably interacted with TCDD in determining certain health effects (e.g. ischemic heart disease). The results reported and discussed in the session do not probably provide a conclusive evidence of the long-term effects of the Seveso accident on the exposed subjects. But the challenge taken 30 years ago is still open: follow-up studies are continuing and a number of molecular epidemiology investigations are under way. These will probably contribute to bridging the existing gap in knowledge about human toxicity of TCDD and about long term sequelae on human health of chemical accidents.

WS1-02 EXPOSURE ASSESSMENT IN SEVESO

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In the years following the July 10, 1976, Seveso incident several epidemiologic investigations were undertaken. Initially all of these used as their exposure index whether one lived or visited the various zones in around the plant site during or shortly after the incident. In 1987 researchers at the U.S. Centers for Disease Control and Prevention (CDC) visited Italy and met with scientists there to discuss the availability of a method and its ability to measure 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), the presumed etiologic agent, in human serum. This ability was confirmed by using small amounts of serum remaining from medical examinations conducted in 1976 from residents of Zone A, the most contaminated zone. Since that time we have collaborated on several Seveso studies including chloracne, second generation exposure studies, men's reproductive health, teeth abnormalities, and the Seveso Women's Reproductive Study. In this presentation, serum dioxin levels will be provided and compared to levels of dioxin and dioxin-related chemicals found in other human cohorts.

WS1-03 MORBILITY FOLLOW-UP AND ENDOCRINE DISRUPTION OF EXPOSED SUBJECTS

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We monitored (from 1976 to 2005) thousands of people affected by the fallout of TCDD over Seveso on July 10, 1976. Serum samples have been kept frozen and it has been possible after 1988 to measure the TCDD blood lipid content.

The results indicate that:

- Chloracne was the only clinical alteration which partly correlated to TCDD contamination levels, with differing individual susceptibility;
- Miscarriages, perinatal mortality, low birthweight, or congenital malformations did not significantly increase;

Part of the exposed subjects were followed up from 1992 to 2005. The results showed that:

- No pathological laboratory results were related to TCDD levels.
- The half-life of TCDD was longer in women (about 9 years) than in men (about 7.5 years), and much shorter in children.
- A doubled, non-significant risk for endometriosis in women was associated with serum TCDD levels of 100 ppt or higher.
- Among premenartheal women serum TCDD level was associated with a lengthening of the menstrual cycle by 0.93 days.
- The hazard ratio for breast cancer associated with serum TCDD levels was significantly increased to 2.1.
- A skewing of the sex ratio at birth with an excess of females ($p < 0.001$) from parents exposed to TCDD was observed and it was permanently related only to exposure of the father.
- Developmental dental aberrations were registered as well associated with childhood exposure.

WS1-04 MOLECULAR EPIDEMIOLOGY OF DIOXIN ILLNESS IN SEVESO

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Approximately 20 years after the Seveso, Italy accident, we conducted several molecular-epidemiology studies in the exposed and not exposed population to evaluate the impact of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure upon mechanistically based biomarkers of dioxin response in humans. Overall we enrolled 312 healthy subjects, of whom 101 had developed chloracne after the accident. Besides chloracne, no other health conditions were significantly increased in chloracne cases. TCDD levels were still high in the exposed subjects (range: <1.7-475.0 ppt), particularly in females, in subjects who had eaten home-grown animals, and in individuals with older age, higher BMI, and residence near the accident site. We found a negative correlation between plasma IgG concentrations and TCDD levels ($r=-0.35$; $p=0.0002$), and several alterations of gene expression profile in exposed subjects. In particular, we measured the expression of genes in the AhR-dependent pathway, including AhR, aryl hydrocarbon receptor nuclear translocator (ARNT), CYP1A1, and CYP1B1 transcripts, and the CYP1A1-associated 7-ethoxyresorufin O-deethylase (EROD) activity in lymphocytes. AhR mRNA levels in uncultured lymphocytes were negatively associated with plasma TCDD ($p=0.03$). When mitogen-induced lymphocytes were cultured with 10nM TCDD, all AhR-dependent genes were induced 1.2 to 13-fold and were correlated with one another. CYP1B1 and CYP1A1 mRNA expression was modified by CYP variant alleles. Specifically, the CYP1B1 *3 haplotype (L432V) was associated with increased CYP1B1 mRNA expression ($p=0.03$), while the CYP1A1 I462V polymorphism was positively, although not significantly, associated with CYP1A1 expression. We also measured global gene expression in lymphocytes by microarray analyses. Several histone genes were upregulated by dioxin exposure, while a few stress-response, transcription factor, and pro-inflammatory genes were downregulated. Because of the increased incidence of Non Hodgkin Lymphoma (NHL) in Seveso as in other dioxin-exposed populations, we investigated prevalence and frequency of circulating NHL-related t(14;18)-translocations in subjects' lymphocytes. We found that the frequency, but not the prevalence, of t(14;18) translocation-positive cells significantly increased with increasing plasma TCDD (p -trend=0.003). Overall, our findings suggest the presence of long-term effects in the subjects exposed to TCDD after the Seveso accident, which require further investigation for their potential impact on public health, and elucidate the importance of the molecular epidemiology approach to investigate the dose-response profile, mechanisms of action and susceptibility factors contributing to dioxin toxicity in humans.

WS1-05 SEVESO WOMEN'S HEALTH STUDY : A STUDY OF TCDD AND REPRODUCTIVE HEALTH IN A FEMALE COHORT

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2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD) is a known carcinogen and endocrine disruptor. Animal studies have reported reproductive health effects following *in utero* or postnatal TCDD exposure, although there are few studies conducted to confirm these findings in humans.

In 1976, a chemical plant explosion in Seveso, Italy exposed the nearby residents to the highest exposure to TCDD known in humans. Twenty years later, we initiated the Seveso Women's Health Study (SWHS), a retrospective cohort study, to determine whether exposure increased risk for reproductive disease. Women eligible for the SWHS were ≤ 40 years in 1976, had resided in one of the most highly contaminated zones (A or B) and had stored sera collected soon after the explosion. Participation included venipuncture, interview, pelvic examination and ultrasound, and completion of a menstrual diary. Individual serum TCDD exposure was measured by high-resolution/mass spectrometry.

Between 1996-1998, we enrolled 981 women (M=41 years). The median serum TCDD was 55.8 ppt, (range: 2.5 - 56,000). We found no association of \log_{10} TCDD with spontaneous abortion (aOR = 0.8, 95% CI = 0.6, 1.2); birthweight (adjusted beta = -4 grams, 95% CI = -68, 60); or small for gestational age births (aOR = 1.2, 95% CI = 0.8, 1.8), although associations were stronger for pregnancies within the first eight years. For those women who were premenarcheal at explosion, \log_{10} TCDD was associated with a 0.93-day increase (95% CI = -0.01, 1.86) in menstrual cycle length. For those <5 years at explosion, there was a somewhat greater risk for earlier menarche (HR = 1.2, 95% CI = 0.98 - 1.6). We reported a doubled, non-significant, risk for endometriosis among women with TCDD levels ≥ 100 ppt, a doubled risk (HR=2.1, 95% CI =1.0, 4.6) for breast cancer, a non-monotonic dose response relationship for earlier age at menopause, and a decreased risk for fibroids.

WS1-06 MORTALITY OF THE POPULATION EXPOSED TO DIOXIN AFTER THE SEVESO ACCIDENT.

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On July 10th, 1976 a large area north-west of Milan, Northern Italy was contaminated by 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) released after an accident in a factory producing trichlorophenol. The polluted territory was divided in 3 areas based on soil TCDD pollution: A (very high), B (high), R (low). This categorization has been subsequently validated using plasma TCDD levels measured in a cross-sectional survey. Acute effects (chloracne) were clearly manifest shortly after the accident, particularly among young people. Mortality, cancer incidence, molecular, and other epidemiology studies are in progress to investigate the potential long-term health effects. The 15-year cancer incidence and 20-year mortality studies found an increase in lymphatic and hematopoietic cancers among both genders in the highly polluted zones A-B; other cancer risks (lung, rectum) were elevated among men. Mortality from diabetes, respiratory, and cardiovascular diseases was also increased. We extended the mortality follow-up through 2001.

The Seveso cohort is composed of about 278,000 subjects who ever had residence, since the accident through 1986, in 11 adjacent municipalities including the polluted area and a surrounding non-contaminated (non-ABR) zone chosen as reference. Zones A, B, R, and non-ABR include respectively about 800, 5,900, 38,600, and 232,700 inhabitants. The cohort includes subjects resident at the time of the accident (present, 79%), immigrants and newborns (non-present, 21%); the former had presumably higher exposure because they were directly infested by the toxic cloud and may have consumed locally grown contaminated animal and vegetal food in the subsequent days and weeks, before adequate preventive measures were introduced. The ascertainment of vital status and cause of death exploited different data sources including: vital statistics offices of the 11 municipalities; population and mortality databases of Lombardy Region and Local Health Units; postal follow-up for subjects migrated outside Lombardy. Using Poisson regression we calculated rate ratios (RR) for selected causes for each of the A, B, R zones versus reference, adjusted for age and period, separately by gender, presence at the accident, and latency.

Vital status ascertainment was over 99% complete; collection and coding of causes of death is in progress. In the extended follow-up period almost 10,000 additional deaths were recorded. As of 2001 the total number of deaths was 47,592 (25,007 males, 22,585 females). Overall mortality in zones A (121 deaths), B (811), and R (6,307) was not elevated in comparison with the reference. Detailed results for selected causes of death will be presented.

WS1-07 TCDD EXPOSURE AND CANCER RISK. CURRENT KNOWLEDGE

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The carcinogenicity of TCDD has long been established in experimental animals, and an extensive literature exists addressing mechanistic aspects relevant to the carcinogenic process. In animals TCDD, the most potent dioxins congener, is a multisite carcinogen that induces cancer in different organs, species and strains. The association between exposure to TCDD and cancer in humans has been investigated in different subsets of populations including Vietnam veterans, occupationally exposed workers and the cohort of residents in the accidentally contaminated area of Seveso, Italy.

In 1997, the International Agency for Research on Cancer (IARC) classified TCDD as a group 1 carcinogen based on limited evidence in humans, sufficient evidence in animals and mechanistic data indicating the involvement of the Ah receptor present in both humans and animals. The IARC evaluation was mainly based on four highly exposed industrial cohorts with a well characterized exposure, and on the Seveso cohort results. The strongest evidence was seen for all cancers which showed an increased risk in all four industrial cohort. A positive exposure-response was observed in two of them. Results by specific cancer sites were less consistent. Noteworthy were the increased risks for lung cancer and Non-Hodgkin's lymphoma in the highly exposed subcohorts.

Since the IARC evaluation, new data have been published that seem to strengthen the previous evaluation. In particular, further dose-response analyses have been performed in three industrial cohorts (NIOSH, Dutch and Germany cohorts) showing a positive trend for all cancers and a meta-analysis of these same cohorts confirmed a positive and significant trend. The mortality of the Seveso cohort showed increases for all cancers (RR=1.3; 95%CI 1.0-1.7) and lung cancer (RR= 1.3, 95%CI 1.0-1.7) after a longer than 15 years period of follow-up, among men residing in the highly exposed zones (A and B). Lymphopietic neoplasms were consistently increased in males (RR=1.7, 95%CI 1.0-2.8) and females (RR=1.8, 95% CI 1.1-3.2) in those same zones. Although based on a limited number of cases, the Seveso Women Health Study found a positive relationship between TCDD serum level and breast cancer incidence. Overall, the evidence accrued in recent years confirms the 1997 IARC evaluation of dioxin as a human carcinogen.

WS2 SHORT TERM EFFECTS OF WEATHER AND PREVENTIVE STRATEGIES TO REDUCE THE IMPACT OF ACUTE EVENTS ON HEALTH IN EUROPE.

Paola Michelozzi, Klea Katsouyanni

WS2-01 SHORT TERM EFFECTS OF APPARENT TEMPERATURE ON HOSPITAL ADMISSIONS IN EUROPEAN CITIES: RESULTS FROM THE PHEWE PROJECT

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Evidence concerning the impact of temperature on hospital admissions is still limited. One of the objectives of the PHEWE project is to evaluate the short-term health effects of temperature on hospitalisation in 12 cities (Barcelona, Budapest, Dublin, Ljubljana, London, Milan, Paris, Rome, Stockholm, Turin, Zurich and Valencia). Hospital admissions for cardiovascular, cerebrovascular and respiratory causes, meteorological and air pollution data were provided from each city. Analyses were performed for the warm (April-September) and cold (October-May) seasons. Maximum apparent temperature (Tappmax) was used as exposure variable with lag 0-3 in summer and lag 0-15 in winter. A Poisson GEE model was fitted for each city. Assumptions were made regarding no correlation between days of separate seasons and an AR(1) structure within season. The effect of Tappmax was modelled as a regression spline allowing for the data to determine itself. Season models were adjusted by month, day of the week, holiday, air pollution, wind speed, linear and quadratic trend. Summer models include the moving average of total admission counts as an offset to control for population reduction during summer; while winter models include influenza epidemics. City-specific results were pooled into two separate groups of cities, Mediterranean and Northern-Continental cities, using different meta-analytic approaches.

Summer: No effect was observed for cardiovascular and cerebrovascular admissions in all cities. An effect of temperature on respiratory admissions was observed in Stockholm, Milan, Turin and London. A positive association between extreme temperatures and respiratory admissions was observed in the older age groups in Stockholm, London, Rome, Valencia and Milan.

Winter: No effect was observed for cardiovascular and cerebrovascular admissions while a linear, negative relationship was observed between winter temperatures and respiratory admissions in London, Budapest, Rome, Dublin, Paris and Valencia. In most of cities, the highest effect on respiratory admissions was observed in the elderly. Pooled analysis was performed only for respiratory admissions.

Summer: In the Northern-Continental cities a significant positive effect of high temperatures was estimated for the 15-64 and 65-74 age groups; both in Mediterranean and Northern-Continental cities was estimated a positive effect in the 75+ age group.

Winter: A significant effect was observed only in Northern-Continental cities with the highest effect in the 75+ age group.

Results on hospital admissions were not consistent with mortality results. Most of summer mortality is accounted for by out-patient deaths. An association with low and high temperatures was observed only for respiratory admissions but with a large heterogeneity among cities.

WS2-02 STATISTICAL MODELLING OF SHORT TERM EFFECTS OF METEOROLOGICAL VARIABLES ON MORTALITY.

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Epidemiological studies indicate that exposure to extreme meteorological conditions is associated with an increase in mortality. We evaluated the health effects of apparent temperature during warm season (April to September) in 15 European cities participating to the PHEWE project. The aim of this work was to investigate the relationship between exposure and mortality and provide city-specific summary measures of the effect of high apparent temperatures, in order to make straightforward comparison among cities.

All cities provided daily counts of deaths for all causes, cardiovascular and respiratory causes and 3-hourly meteorological data retrieved from the nearest airport weather station. Data on several confounders including other meteorological variables and air pollution variables were also considered. A large variability in climatic characteristics and in mortality was observed in the cities involved.

The city specific analyses were based on a GEE approach (Liang and Zeger, 1986). Daily mortality data were modelled by a marginal Poisson model assuming independence among separate summers and AR(1) correlation structure within summer, according to the results of an exploratory analysis based on dynamic models (Chiogna and Gaetan, 2005). Appropriate parametric terms were included in the model to adjust for time trend, seasonality, day of the week, holiday, air pollution concentration, wind speed and sea level pressure.

First, the exposure-response curve was modelled by using a parametric regression spline. Then we modelled the apparent temperature effect by a "V" shaped function and used the estimated slope above the minimum as an indicator of high apparent temperature effect.

The city-specific thresholds, obtained by Maximum Likelihood approach (Muggeo, 2003) and the slopes were combined using Bayesian meta-analysis techniques.

Distributed lag models were specified to investigate the delayed effect of high apparent temperature and time varying coefficients models were used to check sensitivity of results to different definition of warm season.

City-specific and pooled exposure-response curves show a clear "V" or "J" shape. The effects of high apparent temperature were very consistent among cities and it appeared stronger in Mediterranean cities than in North Atlantic and continental cities. Threshold values appeared to vary among cities, ranging approximately from 20°C (north European cities) to 30° (Athens, Rome and Milan). An excess of risk is concentrated in the first days and some evidence of harvesting was found, in particular for Mediterranean cities. The effect of high apparent temperature is quite constant and limited to the period from June to August for Mediterranean cities and from July to August for North Atlantic and continental cities.

WS2-03 EFFECTS OF COLD WEATHER ON MORTALITY: RESULTS FROM 16 EUROPEAN CITIES WITHIN THE PHEWE PROJECT.

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In the framework of PHEWE study, we investigated the short-term effects of meteorological conditions on daily mortality and morbidity. Data from 16 European cities are used providing daily measurements for meteorological variables. Confounding effects of air pollution and chronological variables were considered. The analysis was carried out separately for warm (April-September) and cold (October-March) period and was focused on the effect of apparent temperature on health. We report here the results related to effects during the cold period.

A hierarchical modeling approach was used. First, regression models were fitted in each city separately to allow specific control for weather and other potential confounders. Results of the individual city analysis were used in a second stage analysis to provide overall estimates.

The city-specific analyses were based on the Generalized Estimating Equations (GEE) approach, assuming Poisson distribution on the outcome. For each participating city, we fitted a model with outcome variable the daily number of deaths and several covariates: apparent temperature, confounders (dummy variables for holidays, day of the week and calendar month, air pollution), other meteorological variables (barometric pressure, wind speed). We assumed that observations during one year were correlated, while observations of different years were independent.

The exposure-response curve between apparent temperature and daily mortality shows a linear relationship with negative slope in cold period. One percent increase in the daily total number of deaths is associated with one degree decrease of apparent temperature ($p < 0.001$). The corresponding increase for the cardiovascular and respiratory number of deaths is 1.4%.

Effect modification due to geographical areas and climatic zones as well as other variables was assessed. Interactive and confounding effects of air pollutants (particulate matter, ozone and NO₂) were also investigated.

The PHEWE results are based on the largest data base used for Europe until today and provide quantitative effect parameters which can be used for prevention and public health policy.

WS2-04 YEARS OF LIFE LOST DUE TO SUMMERTIME HEAT IN 16 EUROPEAN CITIES

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In the context of the PHEWE study of summertime heat-related mortality in 16 European cities, we developed a probabilistic assessment of years of life lost (YoLL) considering joint vulnerability distributions based on:

- data-driven city-specific weather records representing the hottest and coolest summers for the 11 study years, as well as a synthetic assembly of the second hottest temperature for each calendar day of the 11 years by city;
- temperature versus mortality functions, by age-group (15-64, 65-74, and 75+ years) based on posterior city-specific adjustments of Bayesian meta-analyses of Northern and Mediterranean groupings. We assumed that increases in temperature ($T_{max}^{day \rightarrow 0}$) under a threshold do not affect mortality and that the effect is linear above the threshold: besides thresholds estimated on the basis of the full 11 years of data, an alternative threshold, designed to represent a city population less adapted to high temperatures, was constructed from functions describing daily mortality restricted to the three coolest recorded summers. Besides our baseline day $-3 \rightarrow 0$ lag structure, we also inputted a cumulative day 0-30 lag to remove mortality displaced by less than a month from our estimate of excess deaths;
- life tables assuming that hot-day decedents would otherwise have had life expectancies no different than others of their age group as well as life tables modified assuming that hot day decedents were older and/or at greater of heat-related death than others of their age group.

For each city, we applied a Monte Carlo approach based on independent sampling ($N=1000$) to estimate excess heat-attributable deaths by age-group under the temperature and weather versus mortality scenarios described above, followed by age-group specific YoLL estimates.

We estimate <60 excess hot temperature-related deaths/year during 1990-2000 in each of the 16 PHEWE cities among persons aged 15-64 and 65-74. For persons of 75+, we estimate 150-200 excess deaths/year in each of Athens, Barcelona, Budapest, Paris, and Rome. The estimated number of excess deaths in these cities is reduced by 35-60% when those occurring within 60 days of above-threshold temperatures are set aside. Certain cities, Paris and Budapest being examples, appear particularly sensitive to high temperatures. We calculate that aggregate years of life lost due to heat occur in fairly similar proportions for the three age groups once short-term mortality displacement is taken into account.

WS2-05 THE DEVELOPMENT OF HEAT HEALTH WATCH WARNING SYSTEMS FOR FIVE EUROPEAN CITIES: RESULTS FROM THE EUROPEAN UNION PHEWE PROJECT

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The general aim of the PHEWE project is to assess the association between weather and acute health effects (daily mortality and hospital admissions) during the warm season in Europe and to provide information for public health policy on preventive and adaptive actions. One such adaptive action is the development of Heat Health Watch Warning Systems (HSWWS) for the prediction and warning of heat related mortality. This paper will describe the climate science issues associated with the development of experimental HSWWS for London, Paris, Barcelona, Rome and Budapest and specifically address the issue of predictability of weather forecast variables and mortality. Further the paper will highlight the fact that no one single climate-based system for the prediction of heat related mortality can be applied universally across the five experimental cities.

WS3 HOUSING AND HEALTH: EMERGING CONCERNS ASSOCIATED WITH RESIDENTIAL EXPOSURE TO CHEMICALS

John D. Spengler and Gary Adamkiewicz, Harvard School of Public Health

WS3-01 PRESENCES OF PHTHALATE ESTERS IN HOMES

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The search for causative factors causing the increase in asthma/allergies has been ongoing for two decades. Volatile organic compounds or microbially produced compounds that are typically measured indoors have not been able to explain fully the causes of such disease. The focus is now shifting to specific classes of chemical compounds. It has been shown that plasticizers from polyvinyl chloride (PVC)-products may play an important role. A number of other compounds related to water-based paints and some cleaning products have now been shown to influence the allergy trend.

Airborne phthalate esters are widely present at detectable levels in ambient air, and have been recognized as major constituents of indoor air. Their presence in outdoor and indoor environments reflects their large emission rates coupled with moderate atmospheric lifetimes. The total global consumption of phthalate esters is estimated to exceed 3.5 million metric tons/year with di(2-ethylhexyl) phthalate (DEHP) constituting roughly 50% of the market share. Consumption of di-n-butyl phthalate (DnBP) and n-butyl benzyl (BBzP) phthalate, is smaller, but still quite large (each greater than 100,000 metric tons/year). Although DEHP plasticizes numerous products, roughly 95% of the current production is used in PVC where it typically constitutes 30% of PVC by weight. DnBP is used in latex adhesives, as a plasticizer in cellulose plastics, as a solvent for certain dyes and, to a lesser extent than DEHP, as a plasticizer in PVC. BBzP is a plasticizer for vinyl tile, carpet tiles and artificial leather, and is also used in certain adhesives.

The current study presented is a nested case-control study on 198 symptomatic children and 202 healthy controls, including detailed clinical examinations by physicians in parallel with extensive inspections and measurements within the subjects' homes. The cases and controls were selected from the first phase (DBH-Phase I), which was a cross-sectional questionnaire soliciting health and environmental information regarding all 14,077 children ages 1-6 in the county of Värmland, Sweden; responses were obtained for 10,852.

This presentation will investigate potential associations between persistent allergic symptoms in children and the concentration of different phthalates in dust collected from their homes.

WS3-02 DAMP INDOOR SURFACE MATERIALS AND ASTHMA: THE ROLE OF CHEMICAL EXPOSURES

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The purpose of this presentation is to address the question: does dampness and presence of certain surface materials in homes have synergistic effects on the risk of asthma?

There is rather consistent epidemiologic evidence of the role of dampness and molds as determinants of asthma both in children and adults (e.g. Bornehag et al. *Indoor Air* 2001;11:72-86, Jaakkola and Jaakkola, *Adv Appl Microbiol.* 2004;55:309-38.). Indoor dampness may induce asthma through different agents, including molds, bacteria, house dust mites, or increased emission of chemicals from damp materials, e.g. volatile organic compounds (VOC) and degradation products of polyvinyl chloride (PVC) floors. The relative importance of the causative agents may vary in different countries. The mechanisms by which indoor molds cause asthma are not yet well-understood, but several potential mechanisms have been suggested. These include IgE-mediated hypersensitivity reactions to fungal allergens, toxic effects of mycotoxins produced by fungi, and nonspecific inflammatory reactions caused by microbial volatile organic compounds (MVOC) or fungal cell wall components, e.g. 1,3-β-D-glucan and ergosterol.

Some epidemiologic studies have suggested that the risk of asthma and asthma-related symptoms is related to the type of interior surface materials, either textile or plastic. Four recent epidemiologic studies in children conducted in Norway (Jaakkola et al. 1999, Oie et al. 1999), Finland (Jaakkola et al. 2000), Sweden (Bornehag et al. 2004), and Russia (Jaakkola et al. 2004) have provided evidence that presence of plastic surface materials increases the risk of asthma or asthma-like symptoms. There is evidence that dampness enhances, besides microbial growth, also chemical emissions, which may play a role in etiology of asthma.

The role of the synergistic effect of dampness and surface materials could be elaborated by assessing potential joint effects, i.e. whether the effect of the presence of dampness and certain materials is more than could be expected from their independent effects. We elaborated this in a population-based incident case-control study of adult asthma in Finland. The clinically diagnosed cases consisted of 521 adults with new asthma and the controls of 932 adults fulfilling eligibility criteria. The risk of asthma was related to the presence of plastic wall materials (adjusted odds ratio 2.43, 95%CI: 1.03-5.75) and wall-to-wall carpet (1.73; 0.74-4.09), the latter in particular in the presence of mold problems (4.64; 1.11-19.4). More epidemiologic studies are needed to assess the joint effects of dampness and surface materials. Better understanding is needed of the effect of dampness on chemical emission from surface materials.

WS3-03 RESIDENTIAL PESTICIDES USE DURING PREGNANCY AMONG AN INNER-CITY COHORT IN NEW YORK CITY: RESULTANT HEALTH EFFECTS AND AN INTERVENTION TO REDUCE EXPOSURES

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Residential pesticide use is widespread in the U.S. but data are limited on use during pregnancy. Between 1998-2004, we gathered information on pesticide use from 620 inner-city pregnant African American and Dominican women. 87% reported using pest control during pregnancy and 46% reported using higher toxicity methods. Pest problems and pesticide use increased significantly with the level of housing disrepair reported ($p < 0.01$). The organophosphorus insecticides chlorpyrifos and diazinon and the carbamate insecticide propoxur were the pesticides detected most frequently: in 99% - 100% of personal air samples collected over 48 hours from the mother during pregnancy ($n=495$, range 0.1-6000 ng/m³); and in 29% - 55% of blood samples collected from the mothers and/or newborns at delivery ($n=464$, range 0.1 - 63 pg/g). Chlorpyrifos and diazinon exposures decreased significantly following the U.S. Environmental Protection Agency 2001-02 ban on their residential use. Prior to the ban, newborns with the highest cord blood chlorpyrifos levels had significantly lower weight and length at birth ($p < 0.01$) and delayed cognitive ($p=0.02$) and psycho-motor ($p=0.002$) development, as well as increased attentional problems ($p < 0.05$), by age three years. A pilot intervention was undertaken between 2001-04 using integrated pest management (IPM) as a means of reducing residential insecticide exposures during pregnancy. The study included 25 intervention and 42 control homes and consisted of professional cleaning, sealing of pest entry points, application of low toxicity pesticides and education. The potential replacements for the banned organophosphorus insecticides were measured in indoor air samples during pregnancy and in maternal and umbilical cord blood at delivery. Cockroach infestation decreased significantly ($p = 0.016$) among intervention but not control households. Among the intervention group, indoor air levels of piperonyl butoxide (a synergist and indicator of pyrethroid use) decreased significantly following the intervention ($p = 0.016$). Among controls, propoxur levels were significantly lower in follow-up compared to baseline air samples ($p=0.04$). Insecticides levels in blood samples at delivery were lower in the intervention compared to control groups. The difference was significant for 2-isopropoxyphenol (propoxur metabolite, $p = 0.04$), cis-permethrin, ($p = 0.03$), and trans-permethrin ($p = 0.003$) in maternal blood samples and for trans-permethrin ($p=0.016$) in newborn blood samples. These pilot data suggest that IPM that includes home repairs is an effective strategy for reducing both pest infestation levels and the internal dose of insecticides during pregnancy.

WS3-04 ASSESSMENT AND CONTROL OF METALS EXPOSURES IN THE RESIDENTIAL ENVIRONMENT DURING THE EARLY STAGES OF LIFE

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Metals, such as lead, arsenic, and cadmium, are common contaminants at many hazardous waste sites and may pose a particular risk to young children due to differences in behavior and their increased susceptibility for neurodevelopmental impairment. Few studies have collected systematic data on concurrent exposure to multiple metals during the early stages of life or accounted for potential interactions. We conducted a longitudinal, multi-media exposure assessment study at the Tar Creek Superfund Site, a mining-related hazardous waste site contaminated by metals in mining tailings and populated by many residents of Native American descent. The objective was to evaluate the relationship between exposures to metals in the residential environment and biomarkers of absorbed metals dose at various stages of development in order to characterize pathways and sources of exposure. The residential environments of 50 children under 1 year of age were inspected and sampled twice at 6 months intervals. Thirty-six percent of homes lived within the Superfund site boundaries and 14% lived in two high-risk towns. From each home, we collected samples of respirable, airborne particles (PM_{2.5}), house dust, drinking water, yard soil, and food to be analyzed for: lead, zinc, arsenic, iron, cadmium, copper, and manganese. Metal concentrations in ambient air were assessed at three fixed sites and a cascade impactor was used to separate <37 μm fraction into smaller size particles. Although ambient air concentrations for PM₁₀ and PM_{2.5} were less than the EPA standards, metals concentrations in smaller (0.1 – 1.0 μm) particles were approximately three times higher than average (<37 μm) size particles. In addition to the thousands of tons of mine tailings piles scattered throughout the area, the "chat", or the smaller particles of mine tailings, has been used as gravel base for roads, parking lots, and concrete slabs in new home construction. Based on the results of an interview, 20% of residents responded that chat had been used in the foundations of their homes, 26% reported knowing of chat used in neighborhood roads, and over 40% said that chat was used in their home's driveway. This information will be used to design, implement, and evaluate a culturally-based risk assessment and nutritional, behavioral and environmental intervention strategy to reduce children's potential in-home exposures. Results from this research can be used to better understand multi-media exposure pathways and to develop practical approaches for studying complex metals mixtures in the residential environment.

WS3-05 INCREASED BURDEN OF RESPIRATORY DISEASE IN THE FIRST YEAR OF LIFE DUE TO PRENATAL AMBIENT AIR TO POLYCYCLIC AROMATIC HYDROCARBONS, KRAKOW BIRTH COHORT STUDY

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The main purpose of our study was to test the hypothesis that prenatal exposure to immunotoxic PAHs may impair the immune function of the fetus and subsequently may be responsible for an increased susceptibility of newborns and young infants to respiratory infections in the first year of life. The study was carried out in a cohort of 333 newborns in Krakow, Poland followed over the first year of life, for whom data from prenatal personal air monitoring of mothers in the second trimester of pregnancy were available. As health outcomes, the occurrence of respiratory symptoms (runny or stuffed nose, cough with or without cold, difficult (puffed) breathing, wheezing or whistling in the chest irrespective of respiratory infection) and number of medical visits in one-year-old infants were considered. Estimated relative risk of various respiratory health outcomes associated with prenatal PAH exposure was adjusted for potential confounders (gender of child, birth weight, maternal atopy, maternal education as a proxy for the socio-economic status, exposure to postnatal environmental tobacco smoke, and moulds in households) in the Poisson regression models.

Personal measurements of the exposure to PAHs compounds were found to be within rather wide range of 3.3 ng/m³ – 316.4 ng/m³ with the mean of 50.7 ng/m³ (SD: 59.8) and the median level of 24.9 ng/m³. Although gestational age was not different between groups with various exposure levels, however, weight, length and head circumference at birth were significantly smaller in infants from the lower exposure group than in the higher exposed group. Reported postnatal ETS, presence of moulds in the households, reported occurrence of parental atopy and season of birth did not differentiate both groups with higher and lower PAH exposure.

Increased risk related to prenatal PAH exposure was observed for the occurrence of several respiratory symptoms such as barking cough (RR = 4.80; 95%CI: 2.73 – 8.44), wheezing without cold (RR = 3.83; 95%CI: 1.18 – 12.43), sore throat (RR = 1.96; 95%CI: 1.38 – 2.78), ear infection (RR = 1.82; 95%CI: 1.03 – 3.23), cough irrespective of respiratory infections (RR = 1.27; 95%CI: 1.07 – 1.52), and cough without cold (RR = 1.72; 95%CI: 1.02 – 2.92). PAH exposure had an impact on the duration of respiratory symptoms as well. The effect related to PAHs exposure on the occurrence of such symptoms as runny nose or cough was partly modified by simultaneous exposure to postnatal passive smoking. The increased burden of respiratory disease in the first year of life associated prenatal PAHs exposure and higher utilisation rates of doctor consultation in infants suggest the revision of public health policy during and after pregnancy period. The frequent episodes of chest infections in early life can lead to persistent lung damage and a longstanding susceptibility to all forms of lung disease in adulthood.

WS3-06 A COMPARATIVE STUDY OF INDOOR VOC EXPOSURES AND ASSOCIATED CANCER RISK IN FOUR NORTH AMERICAN CITIES

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Recent studies have shown that indoor exposures to volatile organic compounds (VOCs) can significantly contribute to cancer risk. While indoor VOC levels may originate from outdoor sources, exposures to these compounds are typically controlled by emissions from numerous indoor sources, including: building materials, floor and wall coverings, tobacco smoking, consumer products, and volatilization from indoor water use. While a detailed source apportionment can be difficult in this context, the coincident collection of indoor, outdoor and personal samples allows for a determination of the relative contribution of source location(s) for measured compounds. Studies that employ these methodologies can be used to understand exposure pathways, set research priorities and to design interventions focused on risk reduction.

We will present the results from personal exposure studies conducted in four large North American cities: Boston, New York, Los Angeles and Mexico City. These studies utilized personal, indoor and outdoor air sampling methods to assess the relative contribution of indoor and outdoor sources to personal exposures. These exposure estimates were used to estimate cancer risk via inhalation, using published unit risk values. Despite significant ambient sources in large urban areas, indoor VOC sources were shown to contribute a significant portion of cancer risk across these cities. Exposures that contributed significantly to this risk include: 1,4-dichlorobenzene, chloroform and several aldehydes, particularly formaldehyde. For example, in both Los Angeles and New York, indoor sources of these compounds accounted for more than 40% of the total cancer risk, based on personal exposures. These studies highlight the importance of indoor VOC sources as a contributor to health risk.

This comparative analysis will present data on the dominant pathways of exposure, the magnitude of cancer risk from measured exposures and the observed between-city differences that may shed light on controlling variables such as product types, product usage patterns and differences in housing stock.

WM1-0 ASTHMA & ALLERGIES (I)
WM1-0-01 AIR POLLUTION AND THE DEVELOPMENT OF ASTHMA AND ALLERGIES IN THE PIAMA BIRTH-COHORT STUDY

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Background: Within the EU-funded TRAPCA-study, we developed exposure models for traffic-related air pollutants (nitrogen dioxide, particulate matter <2.5 μm in diameter, and "soot") and related it to respiratory and allergic symptoms during the first two years of life in a Dutch and a German birth cohort study. We reported positive associations with wheeze, cough, asthma and respiratory infections.

Objective: To confirm our previous results using data from the Dutch PIAMA birth cohort collected at age 7 years (N=3,500), when asthma can be diagnosed more reliably.

Methods: Exposure to traffic-related air pollution at the participants' birth addresses was estimated with regression models based on air pollution measurements and Geographic Information System (GIS) data. Respiratory symptoms as well as potential confounding variables were assessed by parental questionnaire reports. Associations between air pollution and health endpoints were analyzed by logistic regression with adjustment for potential confounders and expressed as adjusted odds ratios (OR) with a 95% confidence intervals (CI) per 5 μg/m³ increase in particulate matter <2.5 μm in diameter (PM_{2.5}).

Results: At age 7 years, 26% of the parents reported that their child ever had wheezed and 9% reported that their child ever had a doctor's diagnosis of asthma. Most of the wheezing was early transient or intermittent. Exposure to PM_{2.5} at the birth address ranged from 13.54 to 25.16 μg/m³ with a mean of 16.88 μg/m³ and was associated with a significantly increased risk of ever having wheezed and ever having had a doctor's diagnosis of asthma during the first 7 years of life [adj. OR (95% CI)=1.26 (1.02-1.55) and 1.45 (1.05-2.02), respectively]. Associations between PM_{2.5} at the birth address and asthma and wheeze during the past 12 months were also positive but not statistically significant [adj. OR (95% CI)=1.15 (0.66-2.01) and 1.13 (0.76-1.68), respectively]. The same holds for the association between PM_{2.5} and sneezing/runny/blocked nose during the past 12 months and doctor-diagnosed hay fever ever [adj. OR (95% CI)=1.26 (0.99-1.60) and 1.23 (0.76-2.00), respectively]. No association with PM_{2.5} was observed for nocturnal dry cough without a cold (past 12 months), bronchitis (ever and past 12 months), doctor-diagnosed flu/serious cold (past 12 months), and ear/nose/throat infections (past 12 months).

Conclusion: These findings confirm our previous findings of an association between traffic-related air pollution, wheeze and asthma. The fact that associations were stronger for life-time prevalence compared to 12 months prevalence indicate somewhat stronger associations with asthma and wheeze before the age of 7 years.

WM1-0-02 URBAN AIR POLLUTION ASSESSED USING A DISPERSION MODEL RELATED TO ALLERGIC AND RESPIRATORY HEALTH IN CHILDREN

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Introduction: The impact of urban air pollution (AP) on respiratory and allergic health is still debated. This might have been the result of inaccurate classification of exposure. Our cross-sectional study was intended to assess the role of AP modelled using a dispersion model in the prevalence of allergic and respiratory outcomes in children.

Methods: 6,683 children aged 9-11 years recruited between March 1999 and October 2000 from 108 schools randomly selected in 6 French cities underwent a clinical examination including skin prick test to common aeroallergens to assess allergic sensitisation and the standardised protocol of the run test to assess exercise-induced bronchial reactivity (EIB). The prevalence of asthma, allergic rhinitis (AR) and eczema were determined through a standardised questionnaire including the International Study of Asthma and Allergies in Childhood core questions, completed by the parents.

Annual mean concentrations of benzene, VOC, CO, NO₂, NOx, PM₁₀, and SO₂ were calculated, in front of the 108 schools attended by the children, by the validated STREET 5 software, which combines data on regional and local components of AP. STREET contains a database of emissions estimated by the IMPACT 2.0 software developed by ADEME-France and results of ambient concentrations modelled by the WinMISKAM 4.2 3D dispersion model. The input data required were background AP, traffic and dispersion (topography and meteorology) conditions. For each air pollutant, a 2-categories-exposure variable was defined with respect to the median value of the modelled concentrations at school. Statistical analyses were performed using Generalized Estimating Equations.

Results: Adjusted odds ratios (OR) for EIB indicated significant positive associations with all modelled air pollutants (OR=1.7 (95% CI: 1.3-2.1) with SO₂, 1.5 (1.2-1.8) with benzene, 1.3 (1.1-1.7) with PM₁₀), except NO₂. Asthma was significantly related to benzene (1.3 (1.0-1.6)), SO₂ (1.3 (1.0-1.6)) and PM₁₀ (1.3 (1.0-1.6)), AR to PM₁₀ (1.2 (1.0-1.4)), eczema to NO₂ (1.2 (1.1-1.4)) and sensitisation to pollen to benzene (1.2 (1.0-1.5)) and PM₁₀ (1.4 (1.1-1.7)). Positive associations of asthma with VOC and CO, of AR with benzene and SO₂, of eczema with PM₁₀, and of sensitisation to pollen with VOC reached borderline statistical significance. Sensitivity analyses suggested stronger associations between sensitisation to pollen and AP in girls than in boys. Positive associations were more pronounced among long-term resident children (current address for at least 8 years).

Conclusions: Accurate modelization of urban AP shows an augmented childhood prevalence of respiratory and allergic diseases in areas with high concentrations of air pollutants.

WM1-0-03 FINDINGS OF TWO-POLLUTANT MODELS IN A STUDY OF AIR POLLUTION AND ACUTE PRIMARY CARE VISITS FOR RESPIRATORY ILLNESS

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Introduction: Previous epidemiological studies have shown associations between various air pollutants and respiratory illnesses. However, there is a lack of published research regarding the findings of multiple-pollutant statistical models. In this study, we sought to investigate the significance of pollutants in two-pollutant models, especially compared to single-pollutant models.

Methods: The time period of analysis is 8/1/98 through 12/31/02 (53 months). We collected data on acute primary care visits from an electronic data warehouse of a large, metropolitan Managed Care Organization (MCO). Acute visits with a respiratory diagnosis of asthma, upper and lower respiratory infections (URI and LRI) and cardiovascular diseases were included in the analysis. Pollutants included 24-hour measurements of PM_{2.5}, coarse PM (2.5-10 μm), PM₁₀, PM_{2.5} components (acidity, sulfates, OC, water-soluble transition metals and elemental carbon), 10-100 nm PM area (ultra-fines), polar VOCs (OHC); 8 hour maximum ozone; and 1 hour maximum NO₂, CO and SO₂. We also looked at PM_{2.5} and PM₁₀ particulate matter metal components. We modeled the relationship between visit counts for each diagnosis group and air quality metrics using general linear modeling, controlling for temporal trends and meteorologic variables. Moving averages of the 0-2, 3-5 and 6-8 day lagged air quality variables were investigated. After modeling each pollutant individually, we investigated two-pollutant models for each case group, including combinations of pollutants that were individually significant at the .05 level.

Results: Most of our significant findings for the single pollutant models were found for child asthma. These findings included statistically significant (p<.05) positive associations for child asthma with PM_{2.5} elemental carbon and water-soluble metals and PM₁₀. Contrary to the single-pollutant model significance, each of these pollutants was not significant in the two-pollutant models, with one exception: PM_{2.5} elemental carbon remained significant after controlling for PM_{2.5} water-soluble metals. Our presentation will include findings from two-pollutant models for each case group for pollutants that were close to the .05 significance level.

Discussion and Conclusion: Investigation of multi-pollutant models is important, but rarely conducted in air pollution epidemiology research. Some of the reasons for the lack of two or more pollutant models are lack of data on more than one pollutant in many studies, limited knowledge on the environmental and biological interaction of air pollutants, and complicated methodological questions such as appropriate consideration of covariance. It is our hope that this study can contribute to dialogue in the search for methods and hypotheses for future multi-pollutant epidemiological research.

WM1-O-04 ASSOCIATION OF INDOOR ALLERGENS AND MOLD WITH ASTHMA DEVELOPMENT IN CHILDREN

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Introduction: Exposure to indoor allergens has been associated with increased symptoms among asthmatic children. Exposure in the first year of life to indoor allergens might also be associated with the development of asthma. We enrolled a cohort of infants with an asthmatic sibling to investigate this association.

Methods: A cohort of 695 children at risk for asthma was enrolled at birth and followed until age six. Mothers were visited in their homes (age 2-3 months) to obtain baseline information and collect samples to measure indoor allergens (*Der p*, *Der f*, *Can f*, *Fel d*) and mold (total mold count, *Cladosporium* count, *Penicillium* count). Follow up interviews were conducted quarterly to age three and annually to age six to determine asthma symptoms, use of asthma medication, and physician diagnosis of asthma, and to update information on observed mold, pet ownership and smoking in the home. Logistic regression models were used to assess the relationship of early exposure to indoor allergens and mold with two outcomes: asthma symptoms at age six (wheeze, persistent cough, chest tightness and shortness of breath); and physician diagnosed asthma with symptoms or medication use at age six.

Results: At age six, 258 children had asthma symptoms, 206 were using asthma medication and 166 had physician diagnosed asthma with current symptoms. Controlling for child's gender, ethnicity, mother's education, parental history of asthma and smoking in the home, early exposure to measured allergens was not associated with asthma symptoms or asthma diagnosis at age six. Mother's report of observed mold at the home interview was associated with asthma diagnosis at age six (Odds Ratio [OR] =1.80 95% Confidence Interval [CI] 1.17-2.76) Asthma symptoms at age six were associated with both reported mold at the home interview (OR=1.60 CI 1.13-2.26) and reported mold at age five (OR=1.70 CI 1.09-2.64). Substituting measured mold counts at the home interview for reported mold in the analysis, neither total mold count nor *Cladosporium* count was associated with increased risk of asthma diagnosis or symptoms. However, increasing levels of *Penicillium* (1-499 CFU/m³, 500-999 CFU/m³, >=1,000 CFU/m³) measured at the home interview were associated with increasing risk of asthma symptoms at age six (OR=1.13 CI 0.78-1.64, OR=2.28 CI 0.79-6.61, OR=2.71 CI 1.04-7.08).

Conclusion: Exposure to mold, especially *Penicillium*, early in life may be associated with increased risk of asthma development by age six.

WM1-O-05 EFFICACY OF HEPA-CPZ AIR CLEANERS ON UNSCHEDULED ASTHMA VISITS AND ASTHMA SYMPTOMS IN ETS-EXPOSED CHILDREN WITH ASTHMA

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Background: Environmental tobacco smoke (ETS) is a risk factor for asthma exacerbations, but it is unknown if reducing ETS will reduce unscheduled asthma visits or asthma symptoms, especially for older children. There is also uncertainty about the efficacy of high-efficiency particle arresting (HEPA) air cleaners on asthma exacerbations and symptoms.

Objective: To test the efficacy of HEPA-CPZ (HEPA with Activated Carbon, Potassium Permanganate and Zeolite filter inserts) air cleaners on unscheduled asthma visits and asthma symptoms for children with asthma who were exposed to ETS.

Participants: We enrolled 225 children who were 6 to 12 years of age, had doctor-diagnosed asthma and were reportedly exposed to >5 cigarettes per day.

Study Design: We employed a randomized, double-blind, placebo-controlled study design. Children in the Experimental Group received two active HEPA-CPZ air cleaners in their home whereas children in the Control Group received two inactivated (placebo) air cleaners. We used the AAP's Child Health Asthma Survey, a validated survey to measure asthma symptoms.

Results: Of the 225 children in the trial, 110 (49%) were randomly assigned to the Experimental Group and 115 (51%) were assigned to the Control Group. The mean age of children was 8.5 years; 62% were male. Children were exposed to a mean of 14.5 cigarettes per day. Of the 225 enrolled children, 215 (95%) participated in the 12-month follow-up study. At 12 months, there was a significant reduction in unscheduled asthma visits (clinic, emergency visits and hospitalizations) in the Experimental Group compared with the Control Group. Adjusting for baseline visits, the number of unscheduled visits for asthma decreased by 87% from baseline to 12-month follow-up in the Experimental Group compared with a 35% decrease in the Control Group (p=0.043). In contrast, there was no significant difference in exhaled nitric oxide, asthma symptoms (shortness of breath, chest tightness, wheeze, or difficulty sleeping), air nicotine, airborne particulates, serum cotinine or hair cotinine by group assignment.

Conclusions: We conclude that HEPA-CPZ air cleaners led to a significant reduction in unscheduled asthma visits. In contrast, there was no reduction in ETS exposure, asthma symptoms or exhaled nitric oxide by group assignment. Although these results hold some promise for using HEPA air cleaners to reduce unscheduled asthma visits, further study is needed before portable HEPA air cleaners can routinely be recommended to reduce indoor air pollutants or asthma exacerbations.

WM1-O-06 EARLY ENVIRONMENTAL EXPOSURES AND INTRACELLULAR TH1/TH2 CYTOKINE PROFILES IN 24-MONTH OLD CHILDREN IN AN AGRICULTURAL COMMUNITY

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Introduction: The relative proportions of T-helper 1 and 2 cytokines (Th1 and Th2) are thought to be associated with allergic asthma and other immune disorders. Several early life exposures, including allergens and endotoxin, influence the development of a predominant Th1 or Th2 phenotype. Recent data suggest that organophosphate (OP) pesticides also may affect the expression of these phenotypes. Because OP, endotoxin and allergen exposures may be higher in rural populations, we examined the association of environmental exposures during the first year of life with Th1 and Th2 levels in 239 24-month old children in an agricultural community.

Methods: Pregnant women were recruited and interviewed twice during gestation, once following delivery, and when their children were 6, 12 and 24 months of age. Home inspections to assess environmental exposures were conducted during pregnancy and at 6, 12 and 24 months of age. Information gathered at the interviews included demographics (maternal age, education, income), breastfeeding history, indicators of pesticide exposure (home pesticide use, parental agricultural work), and other indoor exposures (cigarette smoke, gas stoves, pet ownership). Signs of mold, cockroaches and rodents were assessed during the home inspection. For a subset of children, 6- and 12-month house dust samples were collected and analyzed for OPs (n=84) and allergens/endotoxin (n=63). Blood samples were collected at 24 months and analyzed for Th1 and Th2 using flow cytometric detection of intracellular IFN-g/IL-4 cytokine expression. Th1 and Th2 levels were calculated as the number of IFN-g positive or IL-4 positive cells, respectively, divided by total CD4 cells. Diagnoses of asthma were abstracted from pediatric medical records by trained reviewers.

Results: Th2 levels at 24 months were significantly higher in children with clinically-diagnosed asthma and with maternally-reported wheezing. In multiple regression analyses, maternal agricultural fieldwork was associated with a 26% increase in Th2 levels (p=0.04), and a gas stove in the home was associated with a 47% increase in Th2 (p<0.01). Exclusive breastfeeding at one month of age and pet ownership were associated with 35.3% (p<0.01) and 34.5% (p=0.01) increases in Th1 levels, respectively. Analyses of the relationships between dust constituents and Th1/Th2 are underway and will also be presented.

Discussion: We have identified associations between T-helper phenotypes at age 24 months and early environmental exposures, including maternal agricultural fieldwork, breastfeeding, and ownership of pets and gas stoves. These data add to the growing body of evidence linking early-life environmental exposures and the expression of immune phenotype.

WM1-O-07 HOME MOISTURE AND ASTHMA SYMPTOMS IN INNER-CITY ASTHMATIC CHILDREN

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Introduction: Numerous epidemiologic studies have reported an association between home dampness and respiratory symptoms. Although not uniformly associated with increased risk, recent reviews suggest that dampness in buildings may result in an increased risk for respiratory symptoms. None of these studies have focused on inner-city homes which are typically older and in poor repair. The purpose of this presentation is to evaluate the association between water/moisture damage and caregiver-reported symptoms in the Baltimore Indoor Environment Study of Asthma in Kids (BIESAK) study cohort.

Methods: The cohort consists of 150 asthmatic and 150 non-asthmatic children living in inner-city Baltimore, MD. Participant ages ranged from 2-6 years old. Estimates of home dampness were determined using caregiver-reports and home inspections performed by a trained assessor. During the home inspection settled dust was collected for allergen analysis (Mus m1, Bla g1, and Der f1/Der p1). Asthma-related symptoms, medication use and health care encounters were assessed using a questionnaire. Results based on cross-sectional analysis at baseline are presented.

Results: Caregiver report of water damage was generally not associated with increased allergen concentration in household dust. In contrast, moisture and/or water damage detected on home inspection was associated with increased Mus m1 allergen in the bedroom ($p=0.001$), TV room ($p=0.002$) and Bla g1 allergen in the bedroom ($p=0.001$), TV room ($p=0.001$) and kitchen ($p=0.03$). There was no association with dust mite allergen. It should be noted that dust mite allergen concentrations were generally low in this population. Caregiver reports and home inspection evidence were not associated with asthma symptoms during the previous 12 months. In contrast, care-giver reports and inspector evidence were both positively associated with having an emergency room visit in the previous 3 months ($p=0.05$ and 0.04 respectively). Home inspector evidence was also associated with increased wheeze with exercise over the previous 2-week period. Increased wheezing, coughing, and waking up at night during the last 2-weeks were not significantly associated with either estimate of home dampness.

Conclusions: Results of this study do not indicate that increased moisture and water damage, based on either self-report or home inspection, are associated with asthma morbidity. However, these results do suggest that increased moisture and water damage is associated with increased mouse and cockroach allergens which have been associated with increased morbidity and might be a source of confounding in the studies that report an association between dampness and respiratory symptoms.

WM2-O AIR POLLUTION LONG TERM EFFECTS

WM2-O-01 ESTIMATING LONG-TERM EXPOSURES TO AIR POLLUTION IN SCOTLAND

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Introduction: One of the most challenging tasks for epidemiological studies on chronic health effects of air pollution is to reliably estimate subjects' long-term exposures. The objective of this paper was to investigate different methodologies to estimate long-term exposures to air pollution for subjects recruited in two large Scottish cohorts, whose residences were geographically dispersed across the central belt of Scotland. These methodologies for estimating exposures involved a combination of imputation and modeling techniques of both monitored data as well as local environmental predictors derived using Geographical Information System, GIS.

Methods: Detailed individual baseline risk factors, including the postcode of residence, among 22,000 Scottish participants were collected during 1970-1976. To obtain their long-term exposures to air pollutants, records of black smoke data from 182 monitoring sites were obtained from the UK National Air Quality Information Archive for the decade 1970-79. However, a substantial amount of data was missing in several sites. Missing daily observations at the black smoke monitoring sites were imputed using a log-linear regression model, taking into account day of the week and seasonal effects after grouping sites into regions.

The first technique, a widely used approach, was to obtain inverse-squared distance weighted measures of the geometric mean estimates of the nearby monitoring sites to estimate long-term exposures for participants. The second proposed technique was based on multivariate spatial smoothing using Semiparametric Additive Model with useful local environmental predictors, LEP (which included altitude, household density within a 250m buffer, distance to nearest major road and distance to edge of urban boundaries). An alternative approach, Multilevel Spatio-Temporal modeling of monthly black smoke and LEP, was also developed. The latter model was capable of estimating coefficients of the LEP in the presence of missing data, and allowed for predictions of the missing values from the fitted model. Maps of predicted average participants' exposures using the three methodologies were produced and compared.

Results: The estimated long-term median exposure levels at the participants' residential addresses for the first two methods ranged from 5.4 to 70.0 $\mu\text{g}/\text{m}^3$ and 3.5 to 48.5 $\mu\text{g}/\text{m}^3$ respectively. Range of participants' exposures for the third method was 4.0 to 55.3 $\mu\text{g}/\text{m}^3$.

Discussion: Results from the first method differed from the other two. The latter two approaches took into account useful air quality indicators to predict participants' exposure levels on a finer scale, which would arguably be better reflections of participants' exposures. This project is funded by the UK Department of Health.

WM2-O-02 A REGISTER-BASED CASE-CONTROL STUDY OF AIR POLLUTION AND MYOCARDIAL INFARCTION

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Introduction: Long-term exposure to air pollution has been associated with an increased risk for cardiopulmonary mortality in cohort studies. The aim of this study is to investigate the association between myocardial infarction (MI) and long-term residential exposure to source-specific air pollution in a large register-based case-control study.

Methods: The study population includes all first events of MI in people aged 15-79 during 1985-1996 from a regional MI-register ($n=45,000$). Population controls were randomly selected from the study base matched on age and sex ($n=507,000$). Individual data on occupation and social class for cases and controls was obtained using historical national censuses of the years 1970, 1975, 1980, 1985 and 1990, and geographical coordinates of home-addresses for the years 1980, 1985, and 1990. Annual air pollution exposure was assessed according to the geographical location of the subject's home addresses for the years 1980, 1985 and 1990 using dispersion models based on historical emission databases according to statistics of changes in traffic and other historical land-use variations. These databases describe emissions of nitrogen dioxide (NO_2), carbon monoxide (CO) and particulate matter (PM_{10}) from traffic, and sulfur dioxide (SO_2) from heating in resolutions of 500×500 m in rural areas and 25×25 m in the inner-city area. Due to lack of reliable historic data, PM_{10} was assessed only for the year 2000, thus assuming constant levels during the whole study period. Air pollution exposure was assessed for 19,793 MI-cases and 192,225 controls with complete address information within the study area during all censuses.

Results: Five-year average residential traffic-related NO_2 -exposure from the 5th to the 95th percentile before study inclusion was associated with an odds ratio adjusted for age, sex and socioeconomic status of 1.08 (95% CI 1.03-1.14) for MI and 1.19 (95% CI 1.02-1.38) for fatal MI. The other pollutant indicators including SO_2 from heating were less associated with MI. Average exposure windows further back in time did not indicate any independent association. Somewhat stronger associations were suggested among those who did not change their home-address between the population censuses.

Discussion and conclusions: The limitations of this study include lack of smoking data and misclassification of exposure due to unknown historical addresses. In conclusion, the result of this study adds some support to the hypothesis that long-term traffic-related air pollution exposure is associated with an increased risk of cardiovascular disease.

WM2-O-03 LONG-TERM EXPOSURE TO TRAFFIC PARTICLES IS ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

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Introduction: Long-term exposure to particulate air pollution has been associated with cardiopulmonary and ischemic heart disease mortality in cohort studies, yet none have evaluated cardiovascular endpoints other than mortality. We previously found a significant relationship between indicators of traffic and acute myocardial infarction (AMI) in a large case-control study. In order to assess whether the observed association was due to traffic particles or other components of exposure to traffic, we investigated the relationship between predicted PM_{2.5} reflectance, a surrogate for traffic particles, and AMI within the same population.

Methods: Over 5,000 confirmed cases of AMI were identified between 1995 and 2003 as part of the Worcester Heart Attack Study, a community wide study examining changes over time in AMI incidence among greater Worcester, MA area residents. Population controls were selected from MA resident lists. We used a novel approach to estimate exposure to traffic particles at each subjects' residence. We constructed a latent variable for traffic particles that was correlated with NO₂ and PM_{2.5} reflectance measurements and was on the same scale as PM_{2.5} reflectance. To estimate exposure to traffic particles at the residential locations, we created a regression model in which the latent variable depended on GIS derived measures of distance to major roadway, elevation, and population density as well as a smooth term for latitude and longitude using a 2 dimensional thin plate spline.

Results: An interquartile range increase in PM_{2.5} reflectance was associated with a 12% increase in the odds of AMI (95% CI 2%, 22%). Adding an indicator of cumulative traffic within 100m of the residence significantly improved the model fit; however, the magnitude of the association with PM_{2.5} reflectance remained unchanged. When only cases of first AMI were considered, there was a positive, but non-significant association between PM_{2.5} reflectance and AMI; (odds ratio=1.07; 95% CI 0.96, 1.19).

Discussion and Conclusions: Long-term exposure to traffic particles significantly increased the odds of AMI. This exposure assessment approach allowed for greater separation of the effects of traffic particles on AMI from that of other aspects of exposure to traffic. The exposure model appears to capture variation in traffic particles on a relatively large spatial scale; alternative approaches may be necessary to capture finer scale variation in exposure.

WM2-O-04 AIR POLLUTION AND ATHEROSCLEROSIS: PROGRESSION OF (RESEARCH USING) INTIMA-MEDIA THICKNESS (IMT)

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Background: Atherosclerosis is the most important cause of cardiovascular disease (CVD) and animal studies suggest that ambient particulate matter (PM) may cause atherosclerosis. In earlier research, we observed significant associations between carotid artery intima-media thickness (CIMT) – an established marker of atherosclerosis – and home outdoor PM_{2.5} among volunteers of two clinical trials (T1&2; N=798) (Künzli et al, EHP 2004). This study has to aims: (1) to replicate results in a different population; (2) to explore for the first time the association between PM_{2.5} and progression of CIMT for future power calculations.

New study: We pooled data from three other clinical trials (T3-5) (N=584); enhanced assignment of exposure to ambient PM_{2.5} in geo-coding residential addresses instead of zip code centroids; and updated the Los Angeles area PM_{2.5} surface, based on air monitoring information, land use regression modeling and Bayesian Maximum Entropy Kriging (Moore 2006). Concentrations at home residences were assigned to each subject ("exposure").

Results: The age ranged from 30 to 89yrs (mean: 59yrs). Among T1&2, results based on the new PM_{2.5} surface were very similar as those based on the published older surface (4.3% and 4.2% difference in CIMT per 10 ug/m³ contrast in PM_{2.5}, respectively, adjusted for sex, gender, education, and income). Associations of PM_{2.5} and CIMT among T3-5 were 4.0% (95%CI: -3.0-12.0%), and 5.2% (0.9-9.5%) among T1-5 (N=1503). Effects were again stronger among women over 65 yrs (10.8; 2.0-19.5%; N=251) and subjects reporting prescription of lipid-lowering treatments (N=114) at study entry (9.6%; -3.6-22.0%). A total of 957 subjects (4 trials) had repeat CIMT measures every 6 months for 2-3 years. While adjusted progression was positively correlated with PM_{2.5}, the coefficients were not statistically significant.

Discussion: The similarity of findings in new independent populations of volunteers using CIMT as an outcome supports further use of this measure of atherosclerosis in air pollution studies. We will discuss the mechanistic background and epidemiological characteristics of CIMT, statistical features of cross-sectional CIMT-air pollution associations and challenges to investigate the progression of atherosclerosis. We discuss the high potential of CIMT as a non-invasive reliable outcome in the investigation of chronic effects of air pollution on atherogenesis in children and adults.

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WM2-O-05 LINKING TOXICOLOGY AND EPIDEMIOLOGY TO ASSESS THE HEALTH EFFECTS OF TRAFFIC-RELATED AIR POLLUTION: RESULTS FROM THE HEPMEAP STUDY

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Introduction

Numerous epidemiological studies have demonstrated associations between ambient air pollution particulate matter (PM) and various human health outcomes. Both epidemiological and toxicological studies suggest a profound role for traffic related particles. The capacity of PM to induce oxidative stress in the lung has been proposed as an important biological mechanism, but this theory has not yet been tested in an epidemiological setting. The HEPMEAP (Health Effect of Particles from Motor Engine Exhaust) study focused on comparing the toxicity of ambient PM collected from sites with established contrast in traffic density, and to integrate these results with results from epidemiological studies.

Methods

Using a high volume air sampler, we collected fine (~0.15 – 2.5 µm) and coarse (2.5 – 10 µm) PM during one year at four different sites in the Netherlands. The sites were chosen to represent locations at which an earlier epidemiological study on respiratory health of children attending schools near highways had been conducted. In addition, PM_{2.5}, PM₁₀, PM-absorbance (soot) and NO₂ was measured using the same methods as used during the earlier epidemiological study. The potency of PM to induce oxidative and inflammatory responses was assessed in a range of in-vitro models, including antioxidant (ascorbate) depletion, DNA degradation for the detection of free radical activity, IL-8 and Arachidonic Acid release. Site-specific averages of toxicity were related to the respiratory health data collected in the original epidemiological study.

Results

Estimated annual average levels of soot and NO₂ during the HEPMEAP study were stable over time and showed clear contrasts among the four sites. There was little difference in PM mass concentrations between the four sites, but that there was a contrast in measures of oxidative stress. When oxidative stress and inflammatory parameters were analysed in relation to the findings from the previous epidemiological study, several of them showed a clear association with respiratory symptoms, allergic sensitisation and bronchial hyperresponsiveness. For some of these endpoints these associations tended to be stronger than the associations with soot and NO₂ concentrations.

Discussion and conclusion

The HEPMEAP study is one of the first studies that aimed to integrate results from toxicology and epidemiology. Results show that PM oxidative activity and release of inflammatory mediators are associated with chronic respiratory symptoms, allergic sensitisation and bronchial hyperresponsiveness. These findings support the plausibility of PM induced respiratory health effects

WM2-O-06 CHARACTERIZATION OF PERSONAL, INDOOR, AND OUTDOOR EXPOSURES TO PARTICULATE MATTER AND ITS COMPOSITION IN NEW YORK CITY AND SEATTLE

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Introduction

Few studies have investigated the composition of particulate matter (PM) in indoor microenvironments and for personal exposures. Two COPD panel studies were conducted in New York City (NYC) and Seattle to characterize the inter-relationship among outdoor, indoor and personal PM concentrations.

Method

In the NYC panel, subjects were followed for 12 consecutive days both in a summer and a winter season (July 2000-January 2001), while in the Seattle panel, subjects were followed in a winter season (October 2002-March 2003). Concentrations of PM₁₀ and PM_{2.5} at their residential outdoor, their residential indoor, a central-monitoring-site, and at their personal breathing zones were measured during 24-hour each day. Elemental composition of the PM samples were measured using x-ray fluorescence (XRF), and elemental carbon contents were estimated using reflectance measurements. Indoor-outdoor-personal concentration correlations were investigated. Multivariate factor analysis based source apportionment techniques were applied to identify contributing sources each day.

Results

For NYC, 176 personal and 366 indoor-outdoor paired PM samples were collected from 9 subjects; for Seattle, 142 personal and 320 indoor-outdoor paired PM samples were collected from 15 subjects. Personal PM₁₀ mass concentrations were 2 times higher for the NYC cohort than for the Seattle cohort (71.4, 52.9 and 23.3 µg/m³, for NYC summer, NYC winter and Seattle winter, respectively). Considerable inter-subject variability of the indoor-outdoor correlations were found by season and by geographic locations ($r=-0.4\sim-0.9$, $r=0.1\sim0.7$, and $r=0\sim0.9$, for NYC summer, NYC winter and Seattle winter, respectively).

In NYC, the identified outdoor sources included soil, oil combustion, transported aerosol, and incineration. In Seattle, soil, marine aerosol, and wood combustion were identified outdoors. In both cities, indoor PM was influenced by outdoor sources, such as oil combustion, and by personal activity sources, such as aerosol generated from inhalation therapy.

Discussion

We found different outdoor sources in NYC and Seattle, and indoor PM was associated with outdoor sources and personal activities. The preliminary results suggest that using elemental contents data can provide better characterization of inter-relationships of outdoor, indoor and personal PM concentrations. The detailed quantitative contribution of each source to total PM mass and the contribution of outdoor and indoor sources to personal exposure, and their inter-relationships at each city, will be presented at the meeting.

WM2-O-07 A COMPARISON OF MULTIPLE IMPUTATION AND OPTIMAL ESTIMATION FOR MISSING AND UNCERTAIN URBAN AIR TOXICS DATA

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Introduction: The presence of missing data can be a major problem in air pollution research, especially in time-series analyses where continuous data sequences may be required or statistically advantageous. The multiple imputation (MI) method is now a well-established technique for analyses of missing data in social research, but environmental applications remain very limited. An alternative to MI method, optimal linear estimators, a weighting by the probability of observing data, is theoretically simple, involves fewer modeling assumptions and is efficient, though sensitive to the choice of error and weighting models. These two methods are evaluated for their robustness in handling missing and uncertain urban air toxics (UAT) data in an application aimed at developing exposure measures for a longitudinal investigation of urgent care utilization for asthma among children.

Methods: UATs including carbonyls and volatile organic compounds (VOCs) were collected on a daily basis at a Dearborn air monitoring site (Michigan) from April 2001 to April 2002. These data included numerous replicates and interlaboratory analyses. From the replicate measurements, error models were derived and incorporated in the optimal estimators. Additional variables incorporated into both MI and optimal estimators, besides VOCs and carbonyls, included other pollutants (PM_{2.5}, PM₁₀) and local surface meteorological observations. The performance of the estimators for different missingness patterns was evaluated using the index of agreement (d_i), correlation coefficient (r), the root mean square error (RMSE), and the mean absolute error (MAE).

Results: A total of 69 VOC and carbonyl compounds were measured. Due to large number of compounds that consistently fell below detection limits, 20 toxic compounds were selected for this study. Several error models were developed for these compounds, e.g., the median absolute relative error was 12% for VOCs and 20% for carbonyls. Preliminary results obtained for benzene with 25% randomly selected missing data indicated that both models gave similar performance, though the optimal linear estimator was slightly outperformed ($d_i=0.87$ vs. 0.84 , $R^2=0.62$ vs. 0.53 , $MAE=0.03$ ppbv vs. 0.17 ppbv). A complete analyses will be presented at the conference.

Discussion: To our current knowledge, this is the first study that examined inter-laboratory comparisons and that utilized imputation techniques for air toxics. Using the error models and imputation methods, a complete data is obtained from which exposure measures are derived for our epidemiological study linking UATs exposures and asthma. The procedures also help to quantify and reconcile uncertainties in air toxics data.

WM3-PD EXPOSURE MODULING
WM3-PD-01 SPATIAL CONSIDERATIONS IN A STUDY OF AMBIENT AIR POLLUTION AND CARDIORESPIRATORY EMERGENCY DEPARTMENT VISITS

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Introduction: A common method for assigning exposure in population-based epidemiologic studies of air pollution is to use measurements obtained from centrally-located monitoring sites. Depending on the spatial heterogeneity of a given pollutant, the size of the study area and its population distribution, use of central site concentrations may inhibit the detection of health effects due to exposure misclassification. We have compiled one of the largest time-series studies of air pollution and emergency department visits ($n > 10.2$ million), with data collected from 1993-2004 from 41 hospitals in a 20-county (16,078 km²) U.S. metropolitan area. Daily air pollution concentrations were measured at several monitoring stations, mostly located centrally in the study area. Together, these health and pollution data provide a unique opportunity to investigate the impact of using local versus central-site exposure values. Here, we explore several approaches for assigning exposures and evaluate their influence on observed epidemiologic associations.

Methods: We consider analyses that: 1) exclude days where local source events influenced measurements at the central monitoring site; 2) use daily population-weighted average air pollution concentrations; 3) model visits from populations that reside within specified capture areas around monitors; and, 4) incorporate spatially-resolved modeled exposures, assigning unique values to each residential zip code centroid. We use pollutant-specific correlations among monitoring sites, information on local sources and meteorological trends to define the size and shape of capture areas. To begin, we defined a 650 km² area to capture 22% of the 20-county population; this area is bordered by a highway that envelopes the inner city and most air monitoring locations. We compared associations between three-day moving average pollutant concentrations and daily counts of visits for patients living in zip codes located inside versus outside the capture area.

Results: Associations were consistent and positive for both particle and gaseous pollutants for patients living inside and outside the capture area. There was, however, some indication of stronger associations between cardiovascular outcomes and specific particle measures (e.g., particle mass, metals and organic carbon, but not sulfate) for patients living closer to the central monitor. Results of other spatial analyses will be presented.

Discussion and conclusions: These findings provide support for using central-site measurements of a number of pollutants of interest to represent exposures over the very large study area. Incorporating more detailed exposure assessment methods, in particular for pollutants that exhibit spatial variability, may improve our ability to describe pollutant health effects.

WM3-PD-02 INTRA-URBAN VARIABILITY OF AIR POLLUTION - MONITORING AND MODELLING OF PM_{2.5}, PM_{2.5-10} AND NO₂.

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This research was undertaken as part of the Border Air Quality Strategy (BAQS), an international agreement between the governments of Canada and the United States. Concerns about air quality in the Windsor – Detroit region have led to a number of air health effects studies being undertaken by Health Canada.

The use of central site monitoring stations for assigning exposure has been cited as a potential source of exposure misclassification. Several of the health studies being undertaken for BAQS by Health Canada are investigating the chronic exposure of children to air pollution, which has required the development of local exposure studies. One of which is the development of an intra-urban monitoring network to measure a variety of ambient air pollutants. This monitoring data is being used for the development of models to predict exposure to outdoor air pollution at an intra-urban scale.

There have been several intra-urban monitoring and modelling studies undertaken in Europe and North America. Land Use Regression (LUR) models that have been developed using similar monitoring data have been used with success in improving exposure estimates. However, most intra-urban monitoring studies have frequently measured only NO₂. Therefore, less data is available for particulate matter on such a scale. This is mainly due to the difficulty of measuring particulates at many locations, which this type of modelling requires.

In Windsor, LUR models have so far been developed for NO₂ using data collected with Maxxam Analytic passive samplers. NO₂ concentrations ranged from 6.9 to 20.2 ppb, with a median of 12.0 ppb and were significantly correlated with distance to the Ambassador Bridge ($p = < 0.0001$), length of expressways and highways within 50m ($p = < 0.0001$) and length of major roads within 100m ($p = 0.0475$) in simple regression analyses. A multiple regression model including proximity to the Ambassador Bridge and proximity to highways and major roads predicted NO₂ concentrations with an $R^2 = 0.77$ on an annual basis.

Measurements of NO₂, PM_{2.5}, as well PM_{2.5-10}, were conducted throughout 4 seasons over a 2-week period in 2005 using low-flow particulate monitors located in the backyards of 50 Windsor residences. The range of PM_{2.5} over the four seasons was 6.4 – 29.3 µg/m³, initial Kriging suggests the border crossing heavily influences the higher concentrations. The LUR model is under development and results will be used to compare the relationships between NO₂, PM_{2.5} and PM_{2.5-10}.

WM3-PD-03 USING BAYESIAN HIERARCHICAL MODELLING TO PRODUCE HIGH RESOLUTION MAPS OF AIR POLLUTION IN THE EU

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Introduction: The APMoSHERE project (Air Pollution Modelling for Support to Policy on Health and Environmental Risks in Europe) is funded by the EU fifth framework program. Amongst its objectives are to produce a detailed (1km) inventory of atmospheric emissions (PM10, SO₂, NO_x, CO) by major sector for the EU. A number of different methodologies are being used to produce the pollution maps, here we concentrate on the use of Bayesian Hierarchical Models.

Methods: Yearly average values of air pollutants from a large number of monitoring sites are modelled within a (hierarchical) dynamic linear framework. At stage one of the hierarchy, observed measurements of the pollutants for any particular year are modelled as a function of the true underlying level, corrupted by measurement error. These true underlying levels are assumed to have structure in both space and time, and this structure is modelled at stage two of the hierarchy. Essentially, the values of the pollutants at any time point are modelled as arising from a multivariate Gaussian random field. This model allows measurements to be estimated not just at each of the observed sites, but also at locations previously unmeasured (together with a measure of uncertainty), allowing the required maps to be created.

Results: Spatial-temporal methods were applied to a subset of the available data, in the UK for 1997-2001 maps produced at the 1km x 1km level (of both predicted values and uncertainty), together with an analysis of the components of variability. A spatial model was used to produce maps at the EU-level for 2001. As an example, for NO₂ at the EU level, significant increases were seen in areas further away from the sea and with higher values areas with warm or hot summers and cooler winters. With decreases observed with increasing altitude. The residual or random variation component of the model accounted for only 2.4% of total variation, with the spatial component 66.6% and the regression coefficients 31%. Similar patterns of variability were observed for the other pollutants, albeit with different combinations of explanatory variables.

Discussion: Results of the Bayesian hierarchical modelling demonstrate clearly its potential as a basis for air pollution mapping. An important advantage of the approach is its ability to treat air pollution as a multi-level phenomenon, with contributions that can be predicted on the basis of monitored concentrations from surrounding sites, carefully selected covariates (especially those representing emission sources, such as land cover or road density, and meteorological factors), and long-range spatial structure.

WM3-PD-04 MODELLED LEVELS OF AIR POLLUTION OUTSIDE HOME AND ANNOYANCE.

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During recent years most studies concerning air pollution and health has focused on relatively rare endpoints as death and hospital admissions, while few has studied different measures of more frequent responses as annoyance reactions. The development of dispersion models has made it possible to describe long-term means with high spatial resolution which gives us better data to describe the relation between air pollution levels outside home and perceived annoyance as well as reported irritative symptoms.

The aim of this study was to establish the relation between modelled levels of air pollution (NO₂) outside home and measures of self reported annoyance.

A questionnaire was sent out to 3000 randomly selected participants, age 16-70 years, in the central parts of two Swedish cities. The questionnaire included several questions concerning annoyance related to different environmental factors, but also questions about asthma and asthmatic symptoms. The initial analysis focused on annoyance related to air pollution (scale from 1-11) and how often the participants perceived the air close to home as irritating (daily/almost daily, sometimes or seldom/never).

In total, 1782 filled-in questionnaires were possible to include in the analysis. The main outcomes were dichotomised and analysed in a logistic regression model adjusted for sex, age, smoking, asthma and city. The results showed that a 1 µg/m³ increase of the modelled levels of NO₂ increased the odds of being classified as highly annoyed of air pollution by 1.13 (95% CI for OR = 1.10-1.17), and the odds of experiencing the air as daily or almost daily irritating with by 1.09 (95% CI for OR = 1.05-1.13).

This study showed a significant association between modelled levels of NO₂ outside home and self reported annoyance. Similar relations have been suggested before but not with the same detailed measures of exposure. Given the fact that the prevalence of annoyance is high relative to other health outcomes and the high resolution of the exposure assessment, these results are especially interesting for using in local scale health impact assessments.

WM3-PD-05 SPATIO-TEMPORAL MODELLING OF EXPOSURE TO AIRBORNE POLLUTANTS

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Introduction: Health consequences of environmental pollution depend on the pollution source; its dispersion and mobility. Given that humans move within their environment and between settings (home, work, leisure), exposures estimates should integrate pathways simultaneously through both space and time. Estimation of exposure is often difficult in environmental epidemiology studies. We present methods for estimating exposure that integrate across the space-time domain of human movement patterns whilst allowing for socio-economic factors over the life course.

Methods: We show how changes in residential locations of 541 women from Teesside interact with the changing industrial landscape over time to generate individual based exposure estimates. We obtained data on life-long residential, smoking and socio-economic history interview. We digitised maps of industrial land use from 1930 to 1990. We abstracted the positions of chimneys from six major polluting industries using them to create maps of indices of exposure. We combined the data on residential locations with exposure indices to derive cumulative life-time exposures.

Results: Pollution sources and types changed considerably over the study period: For example the inverse distance weighting of exposure estimates for metal works had a maximum of 6885 in the 1930s and of 432 in the 1990s. Asbestos and chemical exposure estimates peaked in the 1960s whereas values from waste incineration were highest in the 1990s. Women had been living an average of 56.4 (cases) and 55.3 years (controls) in the area. Given the average age of 65 years this indicated a stable population. However, they were mobile within the study area with an average of six moves. We observed greater mobility in high social classes in early life compared to more moves in low social classes in later life. This individual mobility led to highly skewed exposure estimates for some pollution types.

Discussion: Exposure estimates varied greatly and were depending on personal factors such as changes in address and social class. There is a need to integrate the spatial and temporal information for individuals to obtain precise exposure estimates that are valid proxies of true exposure. Our results suggest that this is particularly important if the health outcomes under study are determined by cumulative exposure. This kind of approach is particularly important if pollution types and sources change dramatically over time as has been the case in many parts of the world.

WM3-PD-06 AIR POLLUTANT EMISSION UNCERTAINTY: ESTIMATION AND AIR QUALITY MODELING IMPLICATIONS

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Nowadays to evaluate air pollution exposure and impact on human health air quality models are frequently used to produce concentration fields. The reliability of model results depends mainly on the quality of the emission inventory. Since the methodology to draw up an emission inventory is for the almost totality of the considered activities based on statistical methods, it is important to quantify the uncertainty of the estimates. Moreover the uncertainty varies from an activity to another (e.g. traffic emissions could have a greater uncertainty than industry emissions) resulting in a spatial distribution of emission uncertainty depending on sources distribution.

The methodology proposed to calculate the spatial distribution of the emission uncertainty and to prepare emission scenarios for air quality models is based on the Montecarlo method: a numerical simulation of the emission distribution is performed once the statistical distributions of the emission parameters have been defined. For each of the parameters involved in emission calculation, both exogenous and endogenous, random values are provided independently by the other parameters to construct a consistent sample of parameter values as many emission estimates. Different distributions can be chosen to simulate each parameter (normal, lognormal, 3-p lognormal, uniform). Assigning the proper distribution and statistical values to the parameters involved in every anthropic and natural activity the overall uncertainty can be calculate by grid mesh. Using emission mean values and the variations provided by uncertainty values different emission scenarios can be defined to consider the correspondent variation of concentration fields.

The proposed methodology was applied to a region for which a detailed emission inventory had been drawn up. Three emission scenarios were created considering the calculated variations ($\langle E_{ij} \rangle$, $\langle E_{ij} \rangle - \Delta(E_{ij})$, $\langle E_{ij} \rangle + \Delta(E_{ij})$) where i and j stay for the pollutant and source) and they were used as input of an Eulerian air quality model. As expected the concentration fields obtained show different patterns.

The model results evidenced the importance to consider the uncertainty of emission estimates for each activity considered in the inventory because of the different errors of each estimate and the different spatial distribution of each type of source.

WM3-PD-07 ESTIMATION OF MINUTE-BY-MINUTE FEV1 DECREMENTS ASSOCIATED WITH MODELED OZONE EXPOSURES

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Introduction: Reliable regulatory projection of population responses to ambient ozone exposure requires (1) exposure modeling which captures the exposures of individuals moving through various microenvironments and activity levels and (2) response models which accommodate changing exposure patterns. New models are now available which meet these criteria. This study links these models, providing lung function changes minute-by-minute, and compares predicted responses to those from published controlled human exposure studies of typical and extreme ambient ozone exposure patterns.

Methods: The U. S. Environmental Protection Agency recently developed an enhanced version of the Air Pollution Exposure Model (APEX) that can provide minute-by-minute estimates of ozone concentration (C) and minute ventilation rate (V_e) for individuals based on time/activity patterns in the Consolidated Human Activity Database (CHAD). In this project, researchers develop a stand-alone exposure module that simulates the operation of APEX using (1) CHAD activity patterns, (2) a mass balance model to estimate microenvironmental ozone concentrations, and (3) energy expenditure rates to estimate V_e. Exposure estimates were input to a dose-response module developed by Smith and McDonnell (1999) from controlled human exposure studies of adults 18-35. For each exposure sequence of minute-by-minute C and V_e values, the model produced a corresponding output sequence of minute-by-minute FEV₁ responses.

Results: Using exposure and response data from controlled human exposure studies, researchers found that the model predicts responses consistent with observations for exposures up to 8 hours in studies at constant C with changing exercise patterns and at constant exertion with changing C.

Discussion/Conclusion: Because of earlier model limitations, previous attempts to project population ozone responses have generally focused on exposures over fixed time periods at constant exertion and ozone concentrations, a substantial oversimplification of most actual individual exposures. The current modeling framework allows estimation of realistic exposures on a minute-by-minute basis for selected population groups. Use of such a model should improve the reliability of risk assessment under current or projected ambient conditions.

WM3-PD-08 INDIVIDUAL SUN EXPOSURE CAN BE ASSESSED USING METEOROLOGICAL SATELLITE MEASUREMENTS.

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Objective: To compare measurements of UVA and UVB exposure of children recorded with personal dosimeters with assessment through a detailed questionnaire and satellite measurements.

Methods: 25 families with one index child participated in the study. Participants filled a questionnaire detailing daily activities, geographical location and circumstances of sun exposure. Corresponding satellite measurements of local UVA and UVB irradiation were obtained from the European database SoDa.

Results: Out of 353 days of sun exposure, 437 episodes were recorded with a dosimeter. Median duration of each session was 2 hours, 62% of exposures occurring between 11 a.m. and 3 p.m.. There was a good correlation between measurements from dosimeter and satellite (r=0.48 for UVA; r=0.40 for UVB, Spearman correlation p<0.0001). Dosimeter records tend to underestimate the total exposure measured from the dosimeter (difference per session: 40Wh/m² UVA, 1.5 Wh/m² UVB). The correlation was better for exposure in the sun (r=0.5 and 0.43 for UVA and UVB respectively), on the beach (r=0.57 and 0.42), at the seashore (r=0.64 and 0.40). Multivariate analysis adjusting for weather, exposure duration, horizontal or vertical use of dosimeter, shade, environment and activity showed that Satellite measurements were only significantly influenced by the weather. Dosimeter records were essentially influenced by the type of use (81% in UVA and 73% in UVB decrease of measure when dosimeter was worn on the belt), exposures in the shade (54% decrease for both UVA and UVB), environment (60% decrease for UVA and 34% for UVB for exposure in the country side). When adjusting for all variables, there was a significant independent correlation between dosimeter and satellite measurements (p<0.0001 for UVA and UVB).

Conclusion: Satellite measurements give a good estimate of individual UVA and UVB exposure, independently of exposure conditions and could be used to estimate actual exposure.

WM3-PD-09 MEASURED AND MODELED PERSONAL EXPOSURES TO VOLATILE ORGANIC COMPOUNDS

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Personal exposures to volatile organic compounds (VOCs) depend largely on the locations in which an individual spends the majority of their time and the concentrations in these locations. Americans spend more than 80% of their time indoors and this time indoors is not only spent in residences but also, for many, spent at work. Personal exposure for a given individual can be considered a time-weighted average of exposures encountered in various microenvironments. Thus, it is possible to estimate overall personal exposure through the use of a model employing concentration data from various microenvironments and time activity information. Many personal exposure modeling studies have included indoor and outdoor residential exposures but do not account for workplace exposures. In this study, the primary goal is to quantify the impact of the workplace exposures on explaining the variance in personal exposure measures. Concentration data for 20 VOCs were collected over a 48 hour period inside and outside of residences and in workplaces for 55 individuals in suburban and urban areas across two seasons. On average, personal concentrations were greater than measured indoor, workplace and outdoor concentrations. Measured indoor and workplace concentrations were similar for most compounds and greater than measured outdoor concentrations. The measured personal concentrations were most strongly correlated with the indoor concentrations for most of the compounds (correlations ranging from 0.5-0.75) with the exception of d-limonene and formaldehyde, which were most strongly correlated with measured workplace concentrations (correlations of 0.62 and 0.77; respectively). A time-weighted exposure model was established for each individual in the study by combining the measured indoor and outdoor residential concentrations and comparing the model with the actual measured personal exposure. The workplace concentrations were then added to evaluate their impact on the mean squared error of the model. The impact of including the workplace concentration varied by compound, but variance was reduced for some of the compounds. A second goal is to determine additional necessary information to predict personal exposures for our study population. If additional variance in the personal exposure estimate remained, typical microenvironmental concentration data from other non-residential microenvironments and activities reported in the time activity surveys were added to the model to better predict personal exposure. Understanding the major contributing microenvironments and activities allows for better classification in epidemiological studies, better models for predicting personal exposures, and targeted exposure and risk reduction strategies.

WM3-PD-10 WITHIN- AND BETWEEN-PERSON VARIATION IN ENVIRONMENTAL CONCENTRATIONS OF METALS, PAHS, AND PESTICIDES MEASURED IN NHEXAS-MARYLAND

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INTRODUCTION: Greater attention to variance components can lead to more efficient characterization of exposure and should be considered in the planning and analysis of exposure studies. Previous analyses of the NHEXAS-Maryland data have reported significant temporal variability in exposure, but analyses have only been reported for a small subset of the chemical compounds that were measured. This presentation extends those analyses to all primary chemicals in each of the three compound classes measured in multiple media in NHEXAS-Maryland.

METHODS: The longitudinal NHEXAS-Maryland studies included up to six sampling events per household in the span of one year. We used mixed-effects models to partition observed variance in exposure-related concentrations into within- and between-personal components. We then estimated the Intraclass Correlation Coefficient (ICC) as the between-person component divided by the total variance.

RESULTS: We observed some consistency in ICCs among chemicals within compound classes. For example, in indoor air, pesticides had a higher ICC (0.86 ± 0.05 , mean \pm standard deviation) than PAHs (0.30 ± 0.09) or metals (0.06 ± 0.07). The same pattern was observed in housedust with ICCs of 0.66 ± 0.09 , 0.49 ± 0.04 , and 0.44 ± 0.11 for pesticides, PAHs, and metals, respectively.

DISCUSSION AND CONCLUSIONS: Quantification of variance components allows sampling schemes to be optimized for future human exposure studies. A large within-person component (*i.e.*, a low ICC) indicates substantial temporal variability, with a large number of samples needed to obtain a reliable estimate of exposure. These results suggest that where information on variance components for a specific chemical in a specific media is not available, a chemical's compound class may provide guidance in selecting sample size and in apportioning resources between numbers of subjects and numbers of repeated measurements.

Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.

WM3-PD-11 A DERMAL ABSORPTION MODEL VALIDATED BY LINKAGE TO A PBPK MODEL FOR CHLOROFORM

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Introduction

Dermal absorption is a significant contributor to chloroform concentrations in the body due to dermal exposure to chlorinated water during bathing and swimming. Because of the complexity of dermal exposure mechanisms and the skin absorption process, dermal exposure has only recently been studied more extensively. Most current mathematical absorption models of the skin take into account only one layer of the skin and/or allow for only a one-time deposition onto the skin. However, we have previously presented a dermal absorption model that accounts for two distinct layers of the skin (*i.e.*, stratum corneum and viable epidermis), time-series exposure events, previous concentration in the skin, and changes in skin concentration with time and depth. This two-layer, time-variant dermal absorption model has been linked to a physiologically-based pharmacokinetic (PBPK) model, allowing body burden estimates and validation of the dermal absorption component by comparison with experimental data.

Methods

The PBPK model was constructed using parameters specific to the experimental subject and to chloroform. Chloroform concentrations in exhaled air from inhalation exposure experiments allowed a strong validation of the PBPK model without the dermal absorption component (experimental data and model output differences < 20%). The two-layer, time-variant dermal absorption model for chloroform was constructed and linked to the PBPK model. To validate the dermal absorption component, the combined dermal-PBPK model was used to simulate dermal absorption of aqueous chloroform, and exhaled air outputs were compared to the experimental data.

Results

The combined dermal-PBPK model outputs were found to be highly dependent on parameters for the dermal absorption model that are difficult to estimate. Diffusivity and partitioning for chloroform in the two layers of the skin can be estimated using various equations based on the chemical characteristics of chloroform. However, each parameter can be estimated using multiple methods, often resulting in drastically different values. For instance, two methods for determining diffusivity in the stratum corneum resulted in a difference of a factor of 10⁴. Such differences alter the shape and amplitude of the output curve.

Discussion

Determining the optimal method for estimating the dermal parameters for our model will be important for a more accurate assessment of the impact of dermal exposure. This is especially important for chloroform, for which dermal exposure is a significant exposure route. The combined dermal-PBPK model can then be used to assess the impact of dermal and inhalation exposures simultaneously, in order to more accurately estimate body burden from bathing and swimming.

WM3-PD-12 DEVELOPMENT OF A CUMULATIVE DERMAL ABSORPTION MODEL BY LINKAGE TO A PBPK MODEL FOR CHLORPYRIFOS AND DIAZINON

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Introduction

In light of the Food Quality Protection Act of 1996, it has become increasingly important to assess cumulative exposure to pesticides having the same toxicological endpoint. For some pesticides, the dermal route might be dominant. Most current mathematical skin absorption models treat the skin as one membrane. However, we have previously presented a dermal absorption model with two distinct membranes (*i.e.*, stratum corneum and viable epidermis). This two-layer, time-variant dermal absorption model has been linked to a cumulative physiologically-based pharmacokinetic (PBPK) model for diazinon and chlorpyrifos, allowing body burden estimates of parent compounds and metabolites.

Methods

Separate PBPK models were developed for diazinon and chlorpyrifos to characterize their body distribution. Additional modules were added to the PBPK models to characterize the common metabolites (dialkyl phosphates (DAPs)) of diazinon and chlorpyrifos. These modules are linked to the main models through metabolism in the liver and blood. The dermal absorption model is linked to the PBPK models through blood flow to the exposed skin. To assess the distribution of common metabolites after cumulative exposure events, the PBPK models for diazinon and chlorpyrifos were linked through their common metabolite modules. Model parameters include diffusivities in skin layers, partition coefficients, physiologic and metabolic parameters. Outputs include time course profiles of blood, urine and tissue concentrations of the parent compounds and metabolites.

Results

Input parameters were estimated utilizing several methods. Validation of linked dermal absorption PBPK models was conducted separately for diazinon and chlorpyrifos. In each case, the model was used to simulate multiple human exposure studies available in experimental literature. In these studies, a known amount of the pesticide was applied to skin, and urine metabolite concentrations were measured over time. For diazinon, with refinement of a few input parameter estimation techniques, both the shape and amplitude of the urine time profile for the metabolites was successfully simulated. In the experimental study dermal absorption resulted in excretion of 1550 nmols of DAPs in 70 hours or 0.47% of the applied dose. Model estimates were 1380 nmols DAPs or 0.42% of applied dose. Similar success was achieved for chlorpyrifos.

Discussion

The validated cumulative dermal absorption PBPK model for chlorpyrifos and diazinon is helpful in assessing the importance of the dermal exposure route. For dermal exposure to chlorpyrifos and diazinon, it can be used to assess their relative contributions to urine metabolite levels. However, simulations are limited by input parameter accuracy and experimental study uncertainty used for validation.

WM3-PD-13 MODELING MIXTURES OF ORGANOTIN COMPOUNDS LEACHED FROM POLYVINYL CHLORIDE PIPES USED IN DRINKING WATER DISTRIBUTION SYSTEMS

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Organotins (OT), principally mono- and di-substituted species of butyltins (BT) and methyltins (MT), belong to a broad class of compounds that cause immune, nervous, and reproductive system effects in rodent bioassays. OT is used as a stabilizer in polyvinyl chloride and chlorinated polyvinyl chloride pipe (PVC). Some of the OT does not bind to the PVC polymer chains and, as a result, unbound OT may migrate out of the pipe into transported drinking waters. Thus, PVC may be a source of human exposure to mixtures of BT and MT. Current toxicity data suggest that a mixtures component method could be used to characterize the potential risk posed by these mixtures and will most likely be based on the assumption of additivity of risks. Given its noted toxicity and potential for human exposure due to increased use of PVC pipe in drinking water distribution systems, OT are of concern to the US Environmental Protection Agency. Preliminary studies have evaluated the quantities of OT released from PVC pipe show that initially a large percentage of OT is released immediately after being placed into service and the concentration declines rapidly with use. These data raise two human OT exposure issues: characterizing exposure levels when pipes are first placed into service and exposure when these same pipes are utilized for extended time-periods. The first issue can be straightforwardly addressed using existing data. Addressing the second issue is more challenging and requires modeling OT concentrations to levels that are significantly lower than currently available detection limits. This study estimated OT concentrations in drinking water as a result of PVC leaching by integrating closed-loop laboratory data of OT leaching rates and concentrations with distributions of water intake rates and body weights. An equation was derived that easily calculates the OT concentrations expected in ug/L given the estimated surface area of any water distribution system, at 1 day, 10day, and lifetime exposure.

WM3-PD-14 DEVELOPMENT OF AN EMISSION SCENARIO DOCUMENT (ESD) FOR NON AGRICULTURAL INSECTICIDES

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Introduction: Emission Scenario Documents (ESDs) describing the sources, pathways and use patterns of chemicals are useful tools to quantify the emissions of chemicals into the environment during their life-cycle. ESDs are used in chemical risk assessments within several regulations (EU new & existing substances, biocides...). Within the framework of the Biocides Directive, the need for the development of an ESD for product type 18 (insecticides, acaricides & products to control other arthropods) was identified. This project, supported by the French Ministry of Ecology has been included in the work plan of the OECD Task Force on Biocides. This ESD covers products used by the general public and professionals, from their preparation to their disposal.

Methods: Questionnaires looking at product types, mode of applications and all other technical information were sent to stakeholders. Furthermore, to estimate releases in the different environmental compartments, a literature survey was conducted.

On the basis of the questionnaires received, a matrix approach was applied to identify all relevant environmental compartments in relation with the characteristics of the treatment (organisms to be controlled, application area) and the device used. Then, specific equations were developed to establish the conditions of use and releases, providing a harmonised basis for estimating the concentration of chemicals in the environment.

Results: A preliminary analysis gave a global picture of the variety of products currently on the market. Spraying is the most frequent method of application for insecticides. The compartments exposed during treatment are different when the product is applied indoors and when it is applied outdoors.

For indoor treatments, depending on the cleaning methods, specific compartments will be targeted in the ESD: waste water when the surfaces are washed and solid wastes when the surfaces are swept.

For outdoor application, two areas (urban and rural) and two settings (residential and large buildings) were considered. Post-application releases are essentially due to leaching from treated surfaces by rainwater.

In all cases, certain parameters were set as default values that are derived from human exposure data or extracted from validated environmental models.

Discussion & Conclusions: The default values were discussed in February 2006 with the OECD expert group. The ESD should allow the implementation of consistent exposure assessments throughout OECD member countries. To complete the ESD, other sub-scenarios (e.g. spraying wasp nests, powder or gel insecticides etc.) will be developed. The strategy will be similar and some default values may be re-used.