Method Discrete compartmental models are defined by a set of ordered states (compartments) reflecting the health status, and can be fully characterised by the set of transition probabilities between each compartment. When defined at the individual level, each participant contributes to the likelihood of the model at each year from the time of entering the initial stage (e.g. birth) to the moment they reach an absorbing state (e.g. death or clinical onset). Model estimation aims at quantifying the transitions ensuring the best reconstruction of the pathological trajectories in each subject, hence adding to the classification problem (discriminating healthy and diseased subjects) a dynamic component (estimating the time of onset).

Individual exposure histories can be summarised through cumulative exposure functions and subsequently plugged into the compartmental framework as parameters of transition probabilities.

Results While these models were initially developed to accommodate data from longitudinal studies, we will illustrate, using lung cancer case control and smoking history data, the validity and utility of such approaches. We will assess the underlying assumptions yielded by this methodological drift and will exemplify the rich statistical inference these approaches are able to provide.

Conclusions We will finally introduce potential extensions over this framework that include omics biomarkers to model genetically-driven susceptibility and/or to identify the stage (s) at which exposure (s) are more likely to mediate their effects.

0410 LONG NIGHT SHIFTS AMONG HEALTH WORKERS AND PHYSICAL AND MENTAL HEALTH: THE INFLUENCE OF ON-SHIFT NAP AND DOMESTIC WORK

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Objectives This presentation during the Shift work Symposium aims to discuss data on physical and mental health among health workers, considering the relevance of on-shift naps and routine housework. In addition, the presentation aims also to analyse the cumulative exposure to night work.

Method Data to be presented are based on several epidemiological studies among nursing teams working at 18 Brazilian public hospitals. Databank includes information on socio-demographic and health. Data on work refers to the allowance (or not) to take naps during the night shift and nap regularity. Occupational history data considers (i) whether day workers have worked at night in the past and for how long and (ii) the reasons for quitting night work among former night workers.

Results The allowance for taking naps was observed in all studied hospitals. On-shift nap is a frequent practice among nursing workers. The analysis of occupational history revealed to be relevant as regards physical and mental health. Among former night workers, those who quitted night work for health reasons are at a higher risk of reporting mental suffering.

Conclusions Housework demands seem to aggravate sleep deprivation related to night work, despite evidences of beneficial effects of on-shift naps on workers' recovery. The specific study of former night workers has revealed to be a fruitful approach in studies on health, obesity included, lifestyle and habits, as well as sleep disturbances. Occupational history is an adequate approach for a comprehensive understanding of the impact of night work on health.

0422 CORONARY ARTERY DISEASE MORTALITY AMONG WORKERS EXPOSED TO CARBON DISULFIDE AND SHIFT WORK AT A CHEMICAL MANUFACTURING PLANT

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Objectives Previous studies at a New York State chemical manufacturing plant reported elevated risks of cardiovascular disease among workers. We updated the mortality experience of 1874 workers employed between 1949 and 2006 through December 31, 2007. We investigated exposures to carbon disulfide and shift work and their association with coronary artery disease.

Method Jobs with carbon disulfide and shift work exposure (≥1 day) were identified among departments and job titles in specific years. Standardised mortality ratios (SMR) compared mortality to the US population, adjusted for gender, race, age, and calendar year. Internal comparisons used directly standardised rate ratios (SRR).

Results Overall, excess deaths were observed for coroanary artery disease (SMR=1.24, 95% CI 1.04–1.48). Most workers exposed to carbon disulfide perfortmed shift work; we evaluated coronary artery disease mortality in groups defined by duration of exposure to these agents. Compared to the US population, statistically significant increases in mortality were observed among workers with both exposures for 90 days or more (SMR=1.36, 95% CI 1.03–1.76), and among workers with fewer than 90 days of both exposures (SMR=1.31, 95% CI 0.65–2.34). Using cutpoints of 4 years (median exposure duration among long-term cases), the results were no longer statistically significant. In internal comparisons, long-term workers exposed to carbon disulfide and shift work for 4 years or more had a near 3-fold increase in coronary artery disease mortality, compared to workers exposed less than 4 years.

Conclusions Excess coronary artery disease mortality confirms earlier results, but further investigation is needed to understand risk factors.

0430 INDIVIDUAL VARIABILITY, FROM CANDIDATE G*E TO GEWIS

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Objectives In the 1990s there were great expectations that the use of markers of genetic susceptibility would allow the identification of new occupational risks, a more complete characterisation of dose-response relationships and improved risk assessment. Several interaction studies were conducted examining candidate genes, for example on isocyanate exposure, genes in immune pathways (e.g. HLAII group) and occupational asthma, or studies on cancer, aromatic amines and the NAT2 gene.

Method Very few replicated in more than one population. Part of the problem was the small sample size and the selective

evaluation of candidate genes/SNPs. The availability of GWAS should, theoretically, solve the second problem. We have very few GEWIS (genome-wide interaction study) on occupational exposures and they suffer even more than candidate-gene studies from sample size and also from lack of available studies for replication.
Results Apart from exposures, GEWIS may help identify new diseases genes since many may only have an effect in combination with exposure. In addition GEWIS should provide a much more complete evaluation of specific pathways, e.g. oxidative stress. The use of a specific pathway-based approach is still valuable if based on biological knowledge. Contrary to major advances brought by molecular epidemiology, studies on gene-environment interactions have proven to be complex and with few well established findings.
Conclusions I will discuss reasons for this, discuss recent changes from the use of genome-wide analyses and compare with earlier approaches based on evaluations of interactions of occupational exposures with few candidate genes. I will provide examples from a recent GEWIS on occupational asthma.

0431 THE CONTRIBUTION OF MOLECULAR EPIDEMIOLOGY TO STUDYING OCCUPATIONAL DISEASE: SOME ACCOMPLISHMENTS TO DATE AND OPPORTUNITIES FOR THE FUTURE

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Objectives There are several contributions that molecular epidemiology can make to the study of occupational disease.
Method These include 1) enhancing the ability to study dose-response relationships; 2) evaluating the biological plausibility that an exposure may be related to an adverse outcome; and 3) providing insight into the underlying biological mechanism of an established or suspected exposure-disease relationship. These goals can overlap at times.
Results There are multiple examples where molecular epidemiology studies have contributed important information about occupational exposures, including instances where such studies contributed data that played a role in determining if a given exposure was causally related to disease. Historically, these studies have complimented classic epidemiological investigations.
Conclusions There are multiple examples where molecular epidemiology studies have contributed important information about occupational exposures, including instances where such studies contributed data that played a role in determining if a given exposure was causally related to disease. Historically, these studies have complimented classic epidemiological investigations.

0432 CAN EXPOSURE-RESPONSE CURVES BASED ON MOLECULAR EPIDEMIOLOGY DATA INFORM THE EXPOSURE-RESPONSE CURVE?

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Objectives Derivation of the exposure-response curve at low (occupational) exposures is often troubled by the fact that within epidemiological investigations power to discern the exposure-response curve (ERC) at low exposure levels is often limited. Conversely, we often observe non-linear exposure-response curves at the higher end of the exposure range which amongst others may be due to metabolic saturation.
Method Derivation of the exposure-response curve at low (occupational) exposures is often troubled by the fact that within epidemiological investigations power to discern the exposure-response curve (ERC) at low exposure levels is often limited. Conversely, we often observe non-linear exposure-response curves at the higher end of the exposure range which amongst others may be due to metabolic saturation.
Results Studies on benzene exposed occupational populations have indicated 1) non-linear production of reactive metabolites at low levels of exposure; 2) non-linear production of benzene-oxide adducts; and 3) non-linear associations between benzene and hematoxicity. This is of particular interest as there have been indications of a possible non-linear association between benzene and leukaemia in epidemiological studies.
Conclusions The evidence on a molecular and clinical level may provide evidence for a possible non-linear association between benzene and leukaemia and provides promise that molecular data can directly be integrated in epidemiological risk analyses to inform ERCs.

0436 IS THE FUTURE IN EPIGENETICS?

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Objectives Is the future in epigenetics?

Epigenetics investigates heritable changes in gene expression that occur without changes in DNA sequence. Several epigenetic mechanisms, including DNA methylation and histone modifications, can change genome function under exogenous influence. Results obtained from animal models indicate that in utero or early-life environmental exposures produce effects that can be inherited transgenerationally and are accompanied by epigenetic alterations. The search for human equivalents of the epigenetic mechanisms identified in animal models is in progress. I will present evidence from human environmental and occupational studies indicating that epigenetic alterations may mediate effects caused by toxic exposures. In these investigations, we have shown that exposures, including air pollution, lead, arsenic, nickel, and PAHs, are associated with altered methylation of human repetitive elements or genes. In recent preliminary studies, we have shown alterations of histone modifications and miRNAs in subjects exposed to metal-rich airborne particles. I will present original data demonstrating that altered DNA methylation in blood and other tissues is associated with potentially related disease, such as cardiovascular disease and asthma. On the basis of current evidence, I will propose possible models for the interplay between toxicants and the human epigenome.
Method Please see above.
Results Please see above.
Conclusions Please see above.