1715a

EPIDEMIOLOGICAL EVIDENCE FOR NON-LINEAR EXPOSURE-RESPONSES FOR OCCUPATIONAL CARCINOGENS

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Many chemicals are classified as known human carcinogens, based at least in part on epidemiological evidence. However, occupational epidemiological studies often lack detailed and reliable individual-level exposure information, and only may be capable of qualitatively indicating increased risk among 'exposed' versus 'unexposed' groups. Although this information might be helpful for hazard identification, it is of limited use for risk assessment. Therefore, many investigators have placed greater emphasis on obtaining measurements and deriving quantitative estimates of individual exposures over time. In addition to facilitating the identification of potentially non-linear exposure response relationships, including exposure thresholds for risk, this information helps improve risk assessments. Evidence of nonlinear exposure-response sometimes aligns with knowledge about the agents' route of exposure, mode of action, metabolism and elimination. Furthermore, the identification and application of sensitive biological markers of exposure can help define groups of workers with exposures that are biologically meaningfully different from those of other groups, allowing more precise characterisation of the risk function and possibly the shape of the underlying dose-response function. For many carcinogens, the exposure-response is becoming clearer, and for some it is not linear. Furthermore, where there is evidence of exposure thresholds, epidemiological data may provide direct evidence of the exposure level where risk is increased, i.e., a meaningful departure from background rates. This presentation will review the epidemiological evidence on several known occupational carcinogens that suggest nonlinear risk functions, drawing on examples such as hexavalent chromium, crystalline silica, ionising radiation, vinyl chloride and benzene. Possible mechanisms that give rise to the observed nonlinear relationships (e.g., production of carcinogenic metabolite, overwhelming clearance pathways or repair mechanisms, etc.) will be discussed, and recommendations on how the integration of evidence from different lines of inquiry holds promise for identifying nonlinear exposure-response relationships for occupational carcinogens.

1715b

DEVELOPING STANDARDISED DEFINITIONS OF PEAK EXPOSURES IN EPIDEMIOLOGIC STUDIES OF OCCUPATIONAL CHEMICALS AND CANCER RISKS

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Introduction Peak exposures, often characterised by short-term high intensities, are well established as major etiological contributors to acute adverse health outcomes. Associations between peak chemical exposures and risk of occupational cancers have been contrasted with observed effects related to more conventional metrics, cumulative exposure and exposure

duration. However, the definitions of peak exposure have been highly idiosyncratic, which complicates data interpretation, risk assessment and ultimately setting occupational exposure standards. Thus, there is a need to develop a standardised epidemiologic framework for defining and assessing peak exposures in occupational epidemiology studies of chemical carcinogens, with consideration of underlying toxicological mechanisms, exposure assessment requirements, and policy implications.

Methods We reviewed and contrasted cancer risk findings for peak and cumulative exposures from influential occupational epidemiology studies of benzene and formaldehyde, both classified by IARC as causes of lymphohematopoietic malignancies (LHM) in humans, and for some other possible chemical carcinogens.

Results There is evidence for a strong association between high cumulative exposure to benzene and AML, but little support for an etiologic relation with peak exposure; in contrast, peak benzene exposure has been associated with risk of myelodysplastic syndrome. Peak, but not cumulative formaldehyde exposure has been associated with various LHM. For styrene, no relationship was seen between number of peaks and several cancers of interest. These patterns may be due to variable definitions of peak exposures or may reflect differences in toxicokinetic and carcinogenic mechanisms of these chemicals.

Discussion A peak exposure should be defined quantitatively in terms of exposure intensity, duration, and frequency of occurrence. Future epidemiologic research should apply standardised definitions that can be applied to existing datasets and in newly initiated epidemiologic studies that are consistent with or shed light on the underlying disease processes.

1715c

EPIDEMIOLOGICAL EVALUATION OF EXPOSURE-RESPONSE RELATIONSHIPS FOR CRYSTALLINE SILICA AND RISK OF SILICOSIS AND LUNG CANCER: IMPLICATIONS FOR REGULATION AND PREVENTION

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Effects of crystalline silica on the respiratory tract have been demonstrated in a large number of epidemiological studies. Crystalline silica is a known occupational carcinogen with the lung as main target organ and can cause silicosis as well as chronic obstructive pulmonary disease (COPD). While these hazards are well characterised, there is an ongoing debate on the quantitative exposure-response relationships for crystalline silica and these respiratory endpoints.

Both for regulative and preventive purposes, the demonstration of an exposure threshold which almost excludes any human health risk would be highly desirable. Another option would be the derivation of an exposure-risk relationship associating a given exposure level with a specific lifetime risk, e.g. for lung cancer. However, chronic inflammation – believed to be a threshold effect – is currently considered as the most likely mechanism relevant for both the development of silicosis and lung cancer, while it is unclear whether silica-induced lung cancer requires the presence of silicosis.

This presentation will review the current epidemiological evidence for the derivation of a threshold with respect to the development of lung cancer and silicosis focusing on high-

quality studies with good quantitative long-term exposure data. Although minor or acute inflammatory effects might occur before the detection of silicosis, low-grade silicosis and lung cancer are the only chronic effects which could so far be assessed with reasonable confidence in epidemiological studies.

The available data would support threshold limit values for occupational exposure to crystalline silica in the range of 50 to 100 $\mu\text{g}/\text{m}^3$ which are already in place in several countries.

1693 MEDICHEM SYMPOSIUM: OCCUPATIONAL AND ENVIRONMENTAL IMPACTS ON THE HUMAN GENOME

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Aim of special session This session explores links between occupational and environmental chemical exposures and gene-level mutations and gene regulation, contributing to disease causation

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1693a THE HUMAN GENOME AND MUTATION SIGNATURES OF ENVIRONMENTAL FACTORS

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The human genome is comprised of sequences of three billion DNA nucleic acids. Analysis of DNA sequencing has improved our understanding of many molecular processes relevant for normal physiology and disease. Genetic alterations are the basis of cancer development and can be divided into germline and somatic mutations. While germline mutations are hereditary, somatic mutations are acquired throughout life as a consequence of DNA replication errors, or from some environmental insult such as smoking, occupational or environmental carcinogen exposures, and ultra-violet irradiation. Analysis of the genomic sequence of tumours can identify mutation signatures specific for some environmental factors and direct guidelines for recommended exposure limits and cancer prevention.

1693b INTEGRATIVE GENOMIC ANALYSIS OF MALIGNANT MESOTHELIOMA CELL LINES DERIVED FROM PATIENTS WITH ASBESTOS EXPOSURE

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Introduction Malignant mesothelioma (MMt) is a rare cancer that occurs in the thin layer of tissue that covers the majority of internal organs (i.e., the mesothelium). Mesothelioma most often affects the tissue that surrounds the lungs (pleura). About 90% of cases are related to exposure to asbestos fibres. The period of latency from the moment of exposure to the development of the disease is very prolonged and typically 40–50 years. Genetic analysis of MMt cells revealed changes possibly responsible for the development and progression of MMt.

Methods High-resolution oligonucleotide array comparative genomic hybridization (aCGH) and spectral karyotyping (SKY) were applied to a panel of MMt cell lines.

Result Numerous recurrent karyotypic abnormalities have been delineated, and heterogeneity of chromosomal rearrangements were detected in MMt cell lines. A whole genome search for homozygous deletions (HDs) produced the largest set of recurrent and non-recurrent HDs for MMt; some genes located there could be new tumour suppressors for MMt. The smallest recurrent HD regions affected genes CDKN2A/CDKN2B, LINGO2, RBF1/A2BP1, NF2, RPL29, DUSP7, CCSE1/FAM190A, LATS2. Integrative analysis revealed that acquisition of numerical and/or structural karyotypic instability allows MMt cells to attain a complete loss of tumour suppressor genes located in 9 p21.3, which is the most frequently homozygously deleted region.

Discussion Chromosomal heterogeneity detected in MMt cell lines points to the presence of structural and numerical chromosomal instability in these cells. It is reasonable to suggest that only with the acquisition of structural or numerical chromosomal instability could MMt cells attain a complete loss of tumour suppressor genes. Aneuploidy of MMt karyotypes as well as the presence of structural and numerical chromosomal heterogeneity makes MMt tumours possible candidates for treatment by anti-cancer drugs that target cells with aneuploid, karyotypically unstable phenotypes.

1693c VARIOUS IMPACTS OF INDUSTRIAL POLLUTANTS ON GENE EXPRESSION

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Environmental Toxicology deals with the deleterious effects of anthropogenic pollutants and ionising radiation on plants, animals, and humans. Specific industrial and agricultural chemicals might cause mutagenic, teratogenic and, carcinogenic expressions of genes. Obviously these outcomes indicate that genetic defense mechanisms failed to overcome or to repair gene damage. Gene expression is regulated by structural and chemical modifications of DNA. Anthropogenic pollutants might interfere with the gene regulatory network. The existence of homologue genes shared by some animals and humans enables us to investigate the pathological effects of pollutants on animal models and to relate these relevant mechanisms to humans. This presentation will demonstrate various deleterious mechanisms of harmful chemicals that cause obesogenic, endocrine disruptive, and carcinogenic effects.