Abstracts

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 nonlinear exposure response relationships, including exposure thresholds for risk, this information helps improve risk assessment. 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.

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 lymphohematopoetic 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.

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 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.

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-