Overarching topics

During the discussions of the agents several issues were raised across agents. These issues were identified and discussed the last day of the meeting, and the results are presented in short paragraphs in the following.

Omics

By Martyn Smith PhD

In the biological sciences the suffix –omics is used to refer to the study of large sets of biological molecules. Through various omic technologies it is now possible to interrogate large sets of biological molecules. Although, the number of omic techniques is ever expanding, the most developed omics technologies are high throughput DNA sequencing, transcriptomics (focused on gene expression), epigenomics (focused on epigenetic regulation of gene expression), proteomics (focused on large sets of proteins, the proteome) and metabolomics (focused on large sets of metabolites, the metabolome). These technologies can be used as biomarker discovery tools in human observational studies or to elucidate mechanisms. Their application has become feasible in recent years due to an increase in the resolution and throughput of omics-based assays along with a lowering of cost. However, their application in occupational and environmental health research has been relatively limited to date. If omics-based assays were applied with appropriate study designs, thorough validation of the markers, and careful interpretation of study results then a bioinformatics database could be built of the human response to different chemical exposures and associated chronic diseases. This database could be useful in many ways for evaluating the risk posed by chemical exposures. For example, by comparing newly tested chemicals to the effects of established carcinogens we could identify potential carcinogens (hazard identification);

establish mechanisms of action by studying the effects of the same chemicals in experimental animals and on human cells *in vitro,* allowing for a better prediction of human carcinogenicity and assessment of carcinogenic mechanisms. Given the sensitivity of –omic analyses, low-dose adverse effects could also be observed and distinguished from high dose phenomena, and if exposures were accurately assessed, dose-response data could be incorporated into risk assessments.

Immune modulation

By Shelia Hoar Zahm PhD

Evidence of *in vivo* or *in vitro* genotoxicity often plays an important role in IARC carcinogenicity classifications. However, immunomodulation, hormonal activity, or chronic irritation (cytotoxicity/mitogenic activity) are properties of some substances known to cause cancer in humans. The importance of these latter modes of action needs to be kept in mind when evaluating compounds that appear to increase risk of cancer in humans but that are not classic genotoxins. For example, it is well established, primarily through studies of medical conditions and medications, that immunosuppression and immunostimulation can play a role in lymphogenesis. One of the compounds reviewed in this document, atrazine, is associated with increased risk of lymphoma, but is not genotoxic. A thorough investigation of its potential immunomodulatory effects may clarify its carcinogenicity potential. Identification and standardization of biomarkers of subtle changes in immune status that predict risk as reliably as gentoxocity markers, such as chromosomal abnormalities and sister chromatid exchanges, may make a valuable contribution to hazard identification.

Oxidative stress in carcinogenesis

By Jane Caldwell PhD, Eileen D. Kuempel PhD, Bernard D. Goldstein PhD

Oxidant damage to cellular DNA, proteins (including the epigenome), and lipids can occur when reactive oxygen species escape cell antioxidant and repair mechanisms. Oxidative stress has been implicated in the etiology of many diseases (e.g., cardiovascular, neurodegenerative, rheumatoid arthritis, diabetes, liver disease) and cancers (e.g., breast, colorectal, gastric, hepatic), including those attributed to exposure to exogenous chemical agents (Valavanidis et al., 2009). The mechanisms proposed include direct genotoxicity as well as tumor promotion; e.g. arsenic and perhaps other metals are thought to promote tumors by causing oxidative stress that interferes with apoptosis. (Shi et al., 2004).

A number of methodological issues present challenges to validation of an oxidative stress biomarker assay (Mayne, 2003). For example, 7,8-dihydro-8-oxo-2'deoxyguanosine (8-oxodG) is an extensively studied oxidative DNA damage lesion; however, the artifactual formation of 8-OHdG in cellular DNA during isolation and hydrolysis procedures has impeded its utility as a marker of oxidative stress (Mangal et al., 2009; Mayne, 2003). Recent advances in the development of a new immunoaffinity purification procedure reportedly now

provide a highly specific method of 8-oxodG analysis (Mangal et al., 2009). Additional methodological issues include highly variable background levels of 8-oxodG, differences in substrate affinities of various reactive oxygen species (relevant in chronic disease in which the key oxidizing species are rarely known), and the need to consider biomarkers of nitration as well as oxidation to assess oxidative stress (Mayne, 2003).

The collection of exhaled breath is a noninvasive procedure that permits repeated sampling of the respiratory tract for various biomarkers of oxidative and nitrosative stress, including nitric oxide (NO) and a number of markers in exhaled breath condensate (EBC), although standardization and validation are still needed especially for EBC (Horvath et al., 2005). Malondialdehyde (MDA) and isoprostanes are lipid peroxidation by-products that have been used widely as indicators of oxidative cell damage. Urinary MDA was reportedly stable under various storage conditions (Lee and Kang, 2008).

Although several studies in humans have shown associations between biomarkers of oxidative stress and airborne particulate exposures (Han et al., 2005; Risom et al., 2005; Barregard et al., 2007; Valavanidis et al., 2009), evidence is still lacking on the role of oxidative stress in human carcinogenesis (Loft and Møller, 2006). Lack of specificity and need for standardized and validated methods indicate that careful evaluation is needed in considering the use of oxidative stress biomarkers in epidemiological studies. As for any other biomarkers, research is needed to examine the relationship between exposure to toxic agents and oxidative stress biomarkers, and between these biomarkers and risk of cancer, while controlling for the many individual factors that contribute to oxidative stress. Guidelines on standardizing the collection and measurement of oxidative stress biomarkers in humans (Horvath et al., 2005; ATS, 1999) will facilitate their effective use in epidemiological studies of human cancers.

Exposure assessment

By Mary Schubauer-Berigan PhD

The agents in Group 2 are likely to require high-quality exposure assessment, conducted within the context of an epidemiologic study, in order to definitively assess their carcinogenicity. This need results from several, often concomitant, factors: 1) the low overall expected excess cancer risk compared to the external population, due to the use of industrial hygiene practices to reduce exposures; 2) the likelihood of exposure to multiple carcinogens with the same potential target organ as the agent of interest; 3) the ability to use biomarkers of exposure and effect to infer carcinogenicity (or lack thereof) based on mechanistic or pharmacokinetic information.

The first factor is illustrated by some Group 1 carcinogens; for example, crystalline silica exhibited relatively low standardized mortality ratios (e.g., 2 or less) for lung cancer compared to the general population, yet evidence for an exposure-response association within the cohort (e.g., Rice et al., 2001) greatly strengthened the evidence base for determining carcinogenicity (Straif et al., 2009).

The second factor is illustrated by the Group 1 agents nickel compounds and cadmium and cadmium compounds. Workers involved in metal refining are generally exposed to several potential carcinogens, but quantitative exposure-response information has permitted an evaluation of the contribution of these compounds to cancer risk, while accounting for other potentially carcinogenic exposures (IARC Monograph Vol. 100C, in preparation).

Di-2-ethylhexyl phthalate (DEHP) found in rubber and plastics manufacturing exemplifies the third factor. Using a biomarker of exposure such as DEHP's metabolite MEHP and its subsequent oxidative metabolites (Silva et al., 2006) gives an indication of internal exposure, a better surrogate for target organ dose than workplace measurements of external exposure. Such information about human exposure and metabolism may be used to infer that a mechanism operative in animals does or does not also operate in humans. Biomarkers of exposure, such as serum TCDD levels, have also been employed in lieu of external exposures to provide evidence of carcinogenicity.

Exposure assessments for epidemiologic studies often require the use of retrospective techniques to make use of historical measurement data to create a job-exposure matrix. To be most successful, this technique relies on the past collection and retention of comprehensive, relevant exposure data. Such data frequently consists of industrial hygiene measurements of air concentrations (either area-wide or in the workers' breathing zone). As mentioned above, cohort-wide collection and analysis of biological samples for exposure biomarkers can be employed to good effect; however, this can be expensive and impractical to conduct. Either technique requires consideration of whether adequate latency exists between the measured exposure and the cancer outcome (frequently, mortality) to permit useful evaluation of risk from the exposure. This limitation may be minimized by using validated biomarkers of early effect in lieu of cancer as an outcome (e.g., as discussed in this paper for indium). Practical limitations such as the inability of researchers to access populations or historical exposure information may hamper the ability to develop quantitative exposure estimates for epidemiologic studies of these Group 2 agents. Employers and government agencies should be encouraged to conduct and make available comprehensive exposure assessments that could be used for current or future epidemiologic studies.

Epigenetics

By David M. DeMarini PhD

Epigenetic events are modifications to DNA or chromatin that result in changes in gene expression or levels of translation of mRNAs to protein but do not involve changes in the nucleotide sequence of DNA. Epigenetic modifications involve three general mechanisms: modification (by methylation, acetylation, etc.) of DNA or histones in chromatin or the binding of microRNAs (non-coding RNAs that are 21-23 bases in length) to homologous sequences in mRNA, resulting in a double-stranded structure that can decrease the production of the corresponding protein. Alterations in gene expression and levels of key proteins are associated with carcinogenesis and are considered an essential component of the mechanisms by which most tumors arise. A number of the chemicals considered in this evaluation are not mutagenic, such as chloroform and atrazine, and others, such as lead or DEHP, are indirect

mutagens. These and other compounds considered here likely induce epigenetic changes that play a key role in their carcinogenesis. Chemicals are not routinely assessed for their ability to induce epigenetic events, and no standardized, validated assays are available for such assessments. However, research is needed to develop and validate assays to detect the various types/mechanisms by which agents induce epigenetic changes. Such assays then could routinely be included along with other toxicity endpoints, such as mutagenicity, to better characterize the carcinogenic mechanisms of agents.

Lymphohematopoietic cancer disease categorization

By Bernard D. Goldstein PhD, Ruth Lunn DrPH, and Elizabeth M. Ward PhD

An important methodological issue in designing epidemiological studies is disease categorization. Inconsistencies among findings from occupational cohort studies for a specific substance may be partially explained by misclassification of disease. Most occupational cohort studies measure cancer mortality, which rely on death certificate. Incidence studies using medical records or biological markers are preferred, especially for cancer such as lymphohematopoietic cancers (LHC), which have relatively high survival rates; the 5-year survival rate for leukemia is 51%, and for non-Hodgkin lymphoma is 65% (Jemal et al., 2009). Disease categorization of LHC is a special concern. Several of the substances discussed in this article are associated with increased risk of LHC cancers, for example the chlorinated solvents (DCM, TCE, and Perc), formaldehyde, styrene, and PCBs. For some substances, there is inconsistency in the types of LHC associated with exposure across studies. Some of this inconsistency may be partially explained by inaccuracies in disease characterization. Similarly, the interpretation of carcinogenic outcome in long term animal studies has generally viewed morphologically distinct hematological cancers as separate endpoints. International codes of diseases (ICD) and the understanding of the biology of these cancers have changed over time (Scott and Chiu 2006), raising questions as to the appropriateness of current approaches to hematological cancer characterization.

The ready availability of hematological tissues in the living human for microscopic and molecular study has led to a rich disease nomenclature based upon descriptive morphology. In recent years there has been growing recognition of the close relationship and overlap of disorders whose morphological diversity conferred seemingly distinct disease names. Examples include the clinical recognition that polycythemia vera, essential thrombocythemia and myelofibrosis are part of a myeloproliferative syndrome, which has in common a clonal origin and an increased likelihood of outcome in acute myelogenous leukemia (AML). More recently a specific mutation, known as JAK2 V617F has been found in almost all patients with these myeloproliferative disorders (Zhan and Spivak 2009). Further, deletions and mutations in the TET 2 gene were recently shown to be present in patients with myeloproliferative disorders, for which they preceded the JAK2 V617F mutation, as well as in some patients with secondary AML, with myelodysplastic syndrome and with chronic myelomonocytic leukemia (Delhommeau et al., 2009). Similarly, a variety of seemingly disparate disorders are now grouped together under the myelodysplastic syndrome, again each one having a large proportion of monoclonal blood cells and an increased likelihood of AML as an outcome. The seemingly straightforward distinction between myelogenous and lymphatic leukemias has been blurred by recognition of hybrid forms in which both

characteristics are present, at times one preceding the other. Initially, secondary leukemia following chemotherapy was thought to occur solely as AML, but modern molecular techniques have recognized that many are in fact acute lymphatic leukemia (ALL) (Snyder et al., 2005). Children with Down's syndrome are at increased risk of developing both ALL and acute megakaryocytic leukemia through a complex interplay of genetic events related to trisomy of chromosome 21 (Kearney et al., 2009). Further, in the most recent reclassification of lymphoproliferative disorders, chronic lymphocytic leukemia and multiple myeloma are now considered subclassifications of non-Hodgkin lymphoma; and individuals with myeloproliferative syndromes appear to be at higher risk for each of these lymphoid neoplasms.(Vannucchi et al., 2009)

The growing recognition of common genotypic origin of hematological malignancies with markedly different phenotypic manifestations suggests the need to re-examine current approaches to lymphohematopoietic disease categorization used in epidemiology and in the interpretation of animal toxicology.

Multiple mechanisms of chemical carcinogenesis

By Martyn T. Smith PhD

Recent advances in scientific understanding of cancer biology and increased appreciation of the multiple impacts of carcinogens on this disease process support the view that environmental chemicals can act through multiple toxicity pathways, modes and/or mechanisms of action to induce cancer. For example, the established Group 1 human carcinogens benzene and arsenic have been shown to cause many different effects from chromosome damage to epigenetic changes, underscoring the need to consider interactions among a carcinogen's multiple modes of action, which may in turn be highly informative of the complex interactions among different carcinogens (Guyton et al., 2009). In addition, the relative importance of a given mode of action may vary with life stage, genetic background, and dose. Recently Guyton et al. (2009) identified several key challenges. First, using even an abbreviated list of key cancer-inducing events, noting that the mechanistic information about even well-studied compounds is incomplete. Despite the large number of publications, covering decades of research, on the IARC Group 1 compounds (e.g.,>4000 publications on aflatoxin B1 with >200 specifically focusing on mechanisms), it is evident that information gaps still exist regarding their effects on some of the postulated key events in carcinogenesis. For other carcinogens, the information gaps are more pronounced; moreover, basic information is completely lacking for tens of thousands of chemicals. In summary, cancer in humans is far too complex a long-term process to conceptualize in terms of one simple mode of action and arises from multiple genetic and epigenetic changes, many of which are difficult to measure in vivo.

Nanoparticles

By Paul A. Schulte PhD

Some of the agents considered in this report consist of or may be produced as particles with at lease one dimension at the lower range of the nanoscale, particularly between 1 and 100 nm. Particles at this size have unique properties that are scientifically and commercially exploitable. They generally have more surface area per unit volume than larger particles of the same composition and are generally more biologically reactive, toxic and possibly carcinogenic than larger sizes. It will be important for investigators to consider particle dimensions in future research and to include particles in the range of 1-100 nm in research when appropriate (Schulte et al., 2009). In some cases, nanoscale materials may need to be evaluated separately from larger particles of the same chemical composition if the nanoscale materials could have different health effects. Critical in investigating the health effects of a nanoscale agent is attention to the metrics used in the research. It may be important to characterize exposure in various ways in addition to mass per unit volume. It may be important to use particle count and surface area as well. Also of importance is to consider the heterogeneity of nanoparticles. A large number of physio-chemical parameters can mitigate biological activity and toxicity and these should be considered in research and in comparing results of studies. Additionally, investigators should consider contaminants in nanoparticles and the degree of agglomeration in assessing exposure and biological effect (Schulte et al., 2009).

Polymorphisms/susceptible populations

By Paolo Vineis PhD

The issue of genetic susceptibility to carcinogenic exposures is complex and delicate for several reasons. First, in spite of the large amount of studies that have been performed on candidate genes, and of the recent wave of genome-wide association studies, the stable and reproducible associations are few. Only recently stringent criteria for a systematic evaluation of the genetic evidence ("Venice criteria") have been developed and, when applied to examples, tend to give rise to a small number of reproducible, stable findings (Ioannidis, 2008; Vineis et al., 2009). One of the best recent examples is ethanol/acetaldehyde and gene variants for ADH (Hashibe et al., 2008): in this case the carcinogenicity for upper aerodigestive cancer seems to be limited to those with the frequent genotypes (the variant genotypes being protective), for genes that are clearly involved in ethanol metabolism. This example is important because the observation ("mendelian randomization") strengthens epidemiological findings lending them credibility. Thus, in special cases genetic susceptibility can be used in the evaluation process to upgrade an exposure. In spite of limited examples, often genetic susceptibility to chemical carcinogens is invoked to claim that more sensitive subpopulations exist. When replicated, associations with gene variants tend to be weak, with relative risks in the order of 1.5.

It is currently almost impossible to establish how many cancers are attributable to genes viz. the environment. Researchers generally agree that less than 5% of cancers are attributable to high-penetrant genes, although little is known for other chronic diseases. In general, we can expect little from genetic screening of the population, apart from limited groups (usually families) with a concentration of high-risk mutations. Two key difficulties arise in genetic testing of populations. One is the availability of specific and effective preventive measures for

the screenees, the absence of which seriously detracts from any screening proposal. The second is the large Number Needed to Screen, which implies that very few people who are screened will benefit; a large NNS also implies a potentially large number of false-positive results and unnecessary treatments (Vineis et al., 2001). To assess the role of a gene-environment interaction and screening in a population we need to know the penetrance of the genetic trait and its frequency. A useful approach is to combine penetrance and frequency by computing the number needed to screen (NNS) in order to prevent one case of cancer. There are examples, in fact, of screening activities characterized by high, or very high, NNS: one is screening for phenylketonuria, a monogenic disease with a frequency of one in 10 000–12 000 in white people; population screening is successful in most western countries. However, this is a particular case, since there is a very effective and non-invasive preventive measure (dietary restriction). No similar example is available for carcinogens.

Small businesses

By Elsebeth Lynge PhD and Avima Ruder PhD

For several of the agents discussed at the meeting, accumulation of additional epidemiologic data is complicated by the fact that exposed workers come primarily from small businesses with a high turnover. As occupational cancer cohorts have traditionally been recruited from large factories, exploitation of new data sources is warranted. For historical cohort studies, the literature provides some examples of rosters for recruitment of workers from small businesses. These include union records (Ruder et al., 2001), workers participating in health surveys (Winter et al., 1990), or workers in biological monitoring programs (Anttila et al., 1998). Computerized census records may also provide information on workers from small businesses (Boffetta et al., 1994), and more detailed information may be obtained if the original census forms are available (Lynge et al., 2006). Agricultural census data may be used to identify farmers (e.g. Kristensen et al., 1996). In countries with national business and pension scheme registers, these data sources may be used for identification of workers from small businesses (Sorensen et al., 2007). Use of the listed rosters for epidemiological studies requires that they have sufficient information on identification (name, date of birth, address at time of recruitment, etc) for the later follow up of the registered workers.

For cross-sectional surveys, study participants may be recruited from numerous small workplaces (Calvert et al., 1998). Recruitment can be difficult because the shop or business owner may act as gatekeeper and effectively bar access to the workers (McKernan et al., 2008). One possible solution would be recruiting currently employed workers outside the workplace. If there were a good validated biomarker for recent exposure, such as end-exhaled breath levels of tetrachloroethylene (PCE) for dry cleaners, workplaces could be bypassed. Potential participants—for example, dry-cleaning operators and spotters--would be recruited through advertisements in the appropriate ethnic press/radio stations to come to a Saturday morning study site. PCE breath analysis would be used to determine eligibility (above a threshold for potentially exposed; nondetectable for potential referents). A half-day of tests and interviews would begin with a medical exam and, for example, for dry cleaners at increased risk of cervical cancer, a Pap test evaluated on site (so further tests could be offered the same day if dysplasia or other positive results were found). Blood would be drawn to test

for PCE level and biomarkers of exposure, genetic susceptibility, and effect. Testing for possible neurological, renal, liver, and other health effects would be included in the exam, depending on costs and funding. An occupational history would be taken (including asking the number of workers at the current job), and questions relative to health and lifestyle would be included. Approaches could be made to some of the shops whose workers participated to do environmental sampling and pre- and post-shift testing of the workers. Shops would only be approached if the workforce was large enough so the participating workers could not be identified, and if the exposures (based on the workers' breath levels) were high enough to merit testing. Data based on volunteers should be interpreted in light of the potential selection bias.

Resources

By Jack Siemiatycki PhD

The present document sets out some recommendations for improving our capacity to prevent cancer by identifying its causes. This report deals only with a small fraction of potentially carcinogenic agents, those for which there is some as yet inconclusive evidence of carcinogenicity; for most other agents there exists little or no evidence one way or another. But even the modest research agenda outlined here will be difficult to achieve given current trends in the research environment. In particular, there has over the past two decades been a precipitous decline in the amount of research produced to address issues of environmental/occupational risk factors for cancer. This has been most evident in epidemiologic research. The proximal cause is that there are fewer epidemiologists working in the area of environmental/occupational etiology of cancer. This is not a place to engage in analysis or speculation on the reasons for this unfortunate trend. Such analysis would have to include but not be limited to consideration of the role of training opportunities, career opportunities, funding opportunities and legal-ethical barriers to accessing human subjects and their personal data. If measures are not taken to stem the decline of this area of research, we will be stuck in the future with the same limited epidemiologic knowledge base we have today. It is imperative that appropriate authorities, and we believe national and international public health agencies should be the prime movers, should take stock of this problem to understand its causes and to find ways of solving it.

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