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

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