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).

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