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

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Views and Expert opinions of an IARC/NORA expert group meeting

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