Molecular Epidemiology: Carcinogen-DNA Adducts and Genetic Susceptibility (44167)

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Abstract. **Molecular epidemiological studies assess individual chemical exposures and genetic susceptibility in order to identify cancer risk. Such studies incorporate the development, application, and validation of biomarkers of cancer risk in order to enhance cancer risk assessments, focus cancer prevention strategies, and elucidate mechanisms of carcinogenesis. Current studies of molecular epidemiology are based upon an understanding of the complex, multistage process of carcinogenesis and interindividual variations in response to carcinogenic exposures. Quantitative methods to measure human exposures to carcinogens continue to improve and have been successfully applied to a number of epidemiological studies. Genetic predispositions to cancer, both inherited and acquired, have been and continue to be identified. The combined approach of associating genetic polymorphisms with carcinogen-DNA adduct measurements, in order to assess cancer risk, is showing considerable promise. It is hoped that, in the future, molecular epidemiologists will be able to develop a risk profile for an individual that includes assessment of multiple biomarkers. The field has the near-term potential to have a significant impact on regulatory quantitative risk assessments, which may aid in the determination of allowable exposures. Molecular epidemiological data may also aid in the identification of individuals who will most benefit by cancer prevention strategies.** [P.S.E.B.M. 1997, Vol 216]

Molecular Epidemiology: Multistage Carcinogenesis and Individual Variation

The field of molecular epidemiology seeks to identify cancer risk based upon individual exposures and inherited susceptibilities to cancer. The overall goals are to develop, apply and validate biomarkers of cancer risk in order to enhance cancer risk assessments, focus cancer prevention strategies and elucidate mechanisms of carcinogenesis. An important approach within molecular epidemiology is to build a relationship among an exposure, susceptibility, and clinical outcome. Rather than simply seeking associations between an exposure and disease, molecular epidemiology examines a number of intermediate endpoints and biological markers of both exposure and carcinogenesis (Fig. 1). Common biomarkers that map the way from chemical exposure to clinical cancer involve the detection of blood carcinogen metabolite levels, carcinogen-DNA adduct levels, mutations in critical genes, changes in cellular morphology, and observation of the development of preneoplastic lesions. Importantly, these biomarkers are postulated to be biologically linked to both the exposure and disease.

Two fundamental principles that underlie current studies of molecular epidemiology relate to the complexity of the carcinogenic process and interindividual variations in response to carcinogenic exposures. Cancer is a complex, multistep process involving the evolution of a normal cell into a neoplasm or heritably altered, relatively autonomous growth of tissue. The classical model of experimental chemical carcinogenesis depicts multiple stages (i.e., initiation, promotion, and progression) leading to the development of a malignant tumor (1, 2). However, it is clear that this classical model is an oversimplification (1–4). The complexity of the carcinogenic process is best illustrated by the numerous events, which must take place in order for a specific exposure to trigger a mutation or epigenetic change that results in a cellular clone with a selective survival advantage. A chemical carcinogen first has to undergo absorption, distribution, and often metabolic activation. For the latter, the amount of the reactive metabolite available for DNA damage results from the action of competing Phase I

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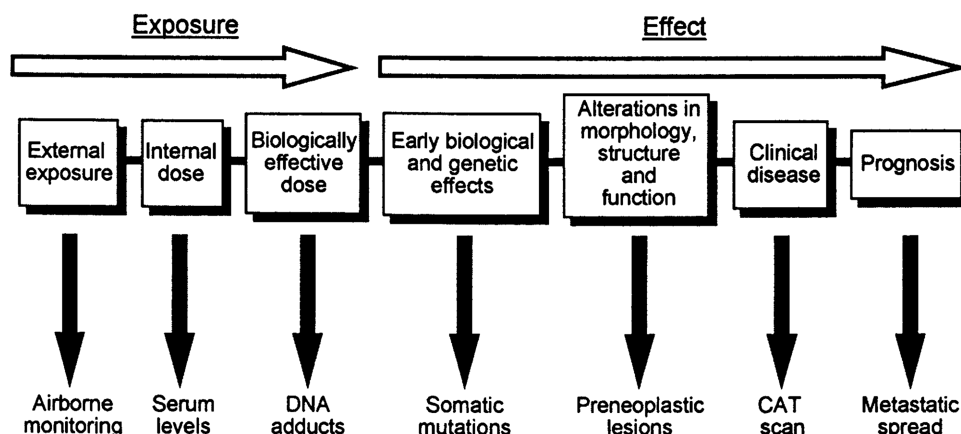

Figure 1. Schematic model depicting the range (from exposure to effect) and types of biomarkers that might be used for cancer risk assessments.

(activation) and Phase II (detoxification) pathways. The persistence of DNA damage is further dependent on DNA repair mechanisms and cell survival. The cell is armed with a battery of repair enzymes capable of correcting DNA damage from single to multiple alterations. If the DNA damage persists or is not repaired properly, it may lead to a clonal genetic mutation. In order for this mutation to lead to a clone with a selective growth advantage, the mutation must be located in a critical gene (i.e., proto-oncogene or tumor suppressor gene) and it must alter that gene's function (1, 2). Finally, the cell must escape other response mechanisms such as programed cell death (i.e., apoptosis). In summary, the multistage process of carcinogenesis is a long and complicated process consisting of multiple pathways. Therefore, the study of a single exposure susceptibility must be undertaken with *a priori* hypotheses and considered against a background of many exposures and risk factors.

The second underlying theme of molecular epidemiology deals with interindividual variation. In almost every step of the multistage process of carcinogenesis, person-to-person differences in cancer susceptibility can be found (1, 2, 5). Investigators and population-based epidemiological studies tend to study the population as if it were homogeneous in its response to carcinogen exposure and/or the carcinogenic process. Cancer risk estimates made by governmental agencies are often based on the assumption that all individuals in a population will respond identically to a specific dose of a carcinogen; however, such an approach might represent an under- or overestimation of risk, at least to particular sensitive or resistant groups or individuals (3, 6).

The emphasis of research in numerous laboratories has been developing assays for determining biologically effective doses of carcinogens and developing, applying, and validating biomarkers of inherited cancer susceptibility. In addition to reviewing the detection of carcinogen-DNA damage and genetic polymorphisms of several drug metabolizing enzymes, this review aims to address multidisciplinary studies that assess the relationship among carcinogen-DNA adducts, inherited susceptibility, and cancer risk.

Carcinogen-DNA Adducts

One indicator for the net effect of exogenous carcinogen exposure and inherited traits for absorption, metabolism, and DNA repair is the carcinogen-DNA adduct. The amount of a carcinogen that reaches the DNA in target tissues is referred to as the biologically effective dose (reviewed in Ref. 7). In the last two decades, our understanding of the physical interactions of chemicals with DNA has advanced immensely. The development of highly sensitive methods to detect macromolecular adducts has made it possible to measure femtomole levels of adducts in human and animal tissues *in vitro* and *in vivo*. The outcome of many of these studies has been an increased understanding of the mechanistic basis of the mutagenicity of many carcinogens. This has provided a rationale for improved biometry and risk assessment, and has also provided information on the mechanism of anticancer drug action (4, 8).

A number of methods have been developed for the sensitive detection of DNA-adducts *in vivo*. These include enzyme immunoassays (9, 10), the [^{32}P]-postlabeling assay (11, 12), a chemical form of postlabeling referred to as adduct detection by acylation with [^{35}S]methionine (ADAM) (13, 14), gas chromatography/mass spectrometry (15, 16), fluorescence spectroscopy (17–19), electrochemical conductance (20, 21), and atomic absorbance spectrometry (22). These methodologies and their application have been reviewed in more detail elsewhere (8, 9, 23, 24). Each method has advantages and disadvantages (Table I) which may vary depending on the type of adduct studied.

[^{32}P] postlabeling is generally the most commonly utilized and most sensitive technique, capable of detecting 1 adduct/10^7–10^{10} normal nucleotides (i.e., as little as one adduct or less per cell). The [^{32}P]-postlabeling assay has

Table I. Methods to Detect DNA Damage[a]

Method	Advantages	Disadvantages
Immunoassays	Sensitive,[b] relatively easy, antibodies useful for immunoaffinity chromatography as a micropreparative step in conjunction with other methods of detection	Potential for cross-reactivity with other similar adducts; requires careful controls with various adduct modification levels; raising antibodies time-consuming
[^{32}P]postlabeling	Generally the most sensitive method, requires small amount of DNA	Labor-intensive; inter- and intralaboratory variability; different labeling efficiencies for different adducts or adduct levels
GC-MS	Specific	Expensive equipment; requires large amount of DNA; may require derivatization
Fluorescence	Specific, relatively easy	Limited to specific adducts; typically requires large amount of DNA
Electrochemical detection	Sensitive, inexpensive, relatively easy	Limited to specific adducts; contamination may be problematic during DNA extraction
Atomic absorbance	Specific, sensitive	Limited to specific adducts (i.e., metals); can only detect amount of total metal but not type of adduct (*e.g.,* monoadduct, cross-link, stereochemistry)
ADAM	Appears to be less variable in labeling efficiency than [^{32}P]postlabeling; seems promising at detecting wide range of adducts	New; may require further validation to be more accepted; has not yet been utilized for many adducts

[a] GC-MS, gas chromatography/mass spectrophotometry; ADAM, adduct detection by acylation with [^{35}S]methionine.
[b] Sensitivity and specificity depend on the affinity of the antibody and the type of assay (e.g., enzyme-linked immunosorbent assay, radioimmunoassay, or ultrasensitive enzyme radioimmunoassay).

been applied in over 100 laboratories to detect DNA adducts from several hundred different compounds, such as arylamines, nitroaromatics, *N*-nitrosamines, polycyclic aromatic hydrocarbons (PAH), quinones, alkylating agents, mycotoxins, and agents generating oxygen free radicals (reviewed in Ref. 11). Such DNA adducts have been detected in relation to occupational exposure, exposure to environmental pollutants, diet, and exposure to clinically used compounds (reviewed in Refs. 11 and 12). For example, recent studies of a highly industrialized region in Poland detected elevated PAH adducts in coke oven workers compared with environmentally exposed individuals (25–27), and higher adduct levels in winter than summer, when less air pollution is present (28).

In our laboratory, we have attempted to increase the specificity of the [^{32}P]-postlabeling assay by combining it with micropreparative steps (i.e., high-performance liquid chromatography and/or immunoaffinity chromatography) (for example, Refs. 19 and 29). Although pre-purification increases specificity, it requires a concomitant increase in the amount of DNA utilized. Further strategies involve use of corroborative, complementary assays, such as synchronous fluorescence spectroscopy (SFS) compared with [^{32}P]-postlabeling (19, 30) gas chromatography/mass spectrometry (31). Even though, technically the [^{32}P]-postlabeling assay does not require detailed knowledge of adduct structure *a priori,* frequently specific adduct standards are synthesized for validation and calibration of the assay (reviewed in Refs. 11 and 12). New developments in DNA adduct detection include the ADAM procedure, a chemical form of postlabeling involving the acylation of nucleoside adducts with an [^{35}S]methionine analog followed by HPLC with radioisotope detection. This approach appears to be a promising new method offering improved sensitivity and reproducibility (13, 14).

Current methods are challenged because of the complexity and multitude of possible exposures in human tissues. Adduct levels from environmental exposures in human DNA approximate the limits of detection and therefore require large amounts of DNA. There is a continual need for further method development. Most assays currently being utilized are too labor-intensive and expensive, and require too much DNA to make these methods practical for screening large numbers of individuals and incorporation into large epidemiological studies. Moreover, corroborative techniques are needed for validation. Several other limitations should be noted about adduct detection. Although smoking has not been associated with cancer of the heart, significant adduct levels have been detected in human heart tissue of smokers (32). In addition, diet, in particular charbroiled food, can be a confounder, as was found in a study of PAH exposure in firefighters (33). Although interindividual variation in adduct levels is expected, Blömeke *et al.* (34) also observed intraorgan variability (30% of the lungs sampled) for 7-alkyl-2′-deoxyguanosine (7-alkyl-dGp) levels in human lung. These results indicate that for most individuals, a random lung sample would be representative of levels throughout the lungs. However, because 30% had widely varying 7-alkyl-dGp adduct levels, a molecular epidemiological study of adduct levels in lung tissue might misclassify adduct burden in some individuals if only one segment or lobe is studied.

Carcinogen-DNA Adducts in Humans

Molecular epidemiological studies have established a relationship of carcinogen exposure to DNA adduct formation (reviewed in Refs. 4 and 35). For example, adducts from PAH, associated with an increased risk of lung and skin cancer, are found in white blood cells of persons exposed to coke oven emissions, tobacco smoke, and urban areas (e.g., from industrial pollution) (25, 36–40). Dietary PAH exposure resulting from the overcooking of meats and fish also result in elevated adduct levels (41, 42). Inhalation of tobacco smoke is among the most important lifestyle risk factors in carcinogenesis, not only resulting in exposure to PAHs, but to over 40 known or suspected carcinogens and mutagens, such as *N*-nitrosamines, ethylene oxide, aromatic amines, and agents that cause oxy-radical damage. Adducts from these agents are correlated with active consumption and passive exposure (43–45), and are associated with an increased risk of lung cancer (46, 47). Putative adducts have been correlated with tobacco use by the [^{32}P]-postlabeling assay in a variety of human tissues such as lung (48–51), cervix (52), bladder (51, 53), breast (54), lymphocytes (55, 56), larynx (57, 58), and placenta (59, 60). Tobacco-specific *N*-nitrosamines, such as the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), form higher hemoglobin adduct levels in smokers compared to nonsmokers (61). DNA adducts, as a result of *N*-nitrosamine exposure, were shown to be elevated in Chinese persons with esophageal cancer (62) and in Japanese persons with liver cancer (63), confirming the risk associated with these adducts and their parent *N*-nitroso compounds.

Genetic Predispositions to Cancer

Numerous host factors, both inherited and acquired, that predispose an individual to cancer have been identified (reviewed in Refs. 4 and 64). The most evident expression of inherited predispositions are familial cancer syndromes. Several rare genetic disorders have been identified such as Li-Fraumeni syndrome, familial bilateral retinoblastoma, bilateral Wilm's tumor, and women with an inherited mutation in the breast cancer susceptibility gene, *BRCA1*, along with various defective DNA repair disorders (e.g., xeroderma pigmentosum, Fanconi's anemia, ataxia telangiectasia, Bloom's syndrome). Such syndromes can lead up to a 1000-fold increased risk of cancer in family members (65). However, such inherited disorders fail to explain cancer in the majority of the population.

Interindividual variation in response to xenobiotics and their potential carcinogenic effects is also mediated by inheritable predispositions (5). Inherited mutations for dysfunctional enzymes generally account for differences in metabolic activation and detoxification; therefore, the level of carcinogen adducts would be expected to vary depending on the metabolic status and may result in placing specific individuals at greater risk of cancer. Other factors in addition to inherited and acquired genetic factors, such as age, gender, race, ethnicity, lifestyle (e.g., tobacco use, alcohol, exercise), diet, preexisting health conditions, and occupation, all may play a role in responses to environmental agents, although the relative contribution of each is unclear (2, 4). While genetic polymorphisms for several enzymes that metabolize environmental carcinogens are reviewed here, other examples exist as well for proto-oncogenes, tumor suppressor genes, and DNA repair enzymes (2).

The cytochrome *P4501A1* gene (*CYP1A1*) is involved in the metabolic activation *via* oxidation of PAHs. *CYP1A1* can be induced upon exposure to compounds present in the environment such as dioxin and PAHs (66, 67), as well as to tobacco smoke (68), and inducibility is notably higher in lung cancer patients than in noncancer controls (69, 70). The first polymorphism to be studied (71) was revealed by an *MspI* restriction fragment length polymorphism analysis and is localized in the 3′-flanking region of the gene. However, this mutation has not yet been correlated with a change in biological function. A second polymorphism (72) at amino acid residue 462 in the catalytic heme binding region involves an A to G base change, resulting in an isoleucine to valine substitution. This alteration was reported to increase catalytic activity (73, 74). However, recent studies by Zhang *et al.* (75) contradict these findings. Although ethoxyresorufin metabolism was slightly increased for the rare valine *CYP1A1* form compared with the common isoleucine form, the rates were similar with benzo[*a*]pyrene as a substrate (75). In Japanese, the presence of the less common allele at the *MspI* site was predictive of the valine substitution (72, 76). In this study (76, 77), there was an overall association with lung cancer and risk in persons who smoked less. The implication of this interaction is that, for persons who smoke less, inherited susceptibilities play an important role, but in extensive smokers the genetics are of lesser importance. There also is one report that associates this polymorphism with increased stage of disease (76). In contrast to Japanese studies, several studies of the *MspI* locus in Western populations, including Caucasians (78–81) and African-Americans (79), have not found an increased lung cancer risk, although such studies are limited due to statistical problems relating to the low prevalence of the "at-risk" allele. For the valine substitution, several studies (80, 81) in northern Europe have thus far not identified an increased risk, although a report from Brazil has found such an association in persons with squamous-cell lung cancer (82). Recently, an association was found between the *MspI* polymorphism and breast cancer risk in African-American women (83), but the valine polymorphism in *CYP1A1* was found to be weakly, but nonsignificantly, associated with breast cancer risk (84). Significantly, an association was found for cigarette smoking, the *CYP1A1* genotype, and breast cancer risk, specifically among lighter smokers (84).

N-Acetyltransferases (NATs) can catalyze the activation or detoxification of aromatic amines, depending on the

substrate. Human NATs are coded by two distinct genes, *NAT1* and *NAT2* (85). *N*-Acetylation of aromatic amines by NATs is generally believed to be involved in detoxification, whereas *O*-acetylation of the *N*-hydroxylamines is an activation step that can lead to aromatic amine-DNA-adducts (85). Polymorphisms of *NAT2* due to germline point mutations in the coding regions determine rapid and slow acetylator phenotypes. An increased risk of bladder cancer in slow acetylators, in particular slow acetylators who are occupationally exposed to aromatic amines, has been observed (85, 86). In a recent breast cancer case-control study, women who had the slow acetylator genotype displayed a dose-response effect for risk from cigarette smoking (87). *NAT1* has recently been shown to be polymorphic as well (88–90), and the *NAT1**10 polymorphism (rapid acetylator) was shown to be associated with risk of colorectal and bladder cancer (91, 92).

Glutathione-*S*-transferases (GSTs) catalyze the conjugation of the thiol containing tripeptide glutathione to electrophilic species, including various carcinogens and drugs, creating a more hydrophilic, less reactive species that can be excreted (93). A polymorphism in *GSTM1* results in a deletion of the entire gene (94). About 50% of the Caucasian population are homozygous for the null allele of this gene and therefore lack *GSTM1* enzymatic activity (95). In addition, the *GSTM1* null genotype shows much variability between different ethnic groups (96). Phenotypically, using cultured blood cells and *trans*-stilbene oxide conjugation, this polymorphism has been related to lung cancer risk in several studies (97, 98), although not consistently (99). The lack of activity also has been associated with increased PAH-DNA adducts in human lung tissue (100), sister chromatid exchange formation (101, 102), and mutagenicity of human lung microsomes in the Ames' assay (103). The application of PCR to the study of this gene has revealed an association of the null genotype with lung cancer in several Caucasian groups (98, 104, 105), especially squamous-cell cancers (104, 105), although some studies have not found such an association (106). There also is a report of an overrepresentation of the null genotype in European women with squamous-cell lung cancer (80). In a recent report by London *et al.* (107), the risk for lung cancer was seen only in persons with squamous-cell cancer and those with less than 40 pack-years of smoking; however, considerable inconsistencies are present in the literature. In addition to lung cancer, the *GSTM1* null genotype has been suggested to play a role in bladder cancer in smokers (95). No association has been found between the *GSTM1* null genotype and breast cancer risk (84, 108).

DNA-Adducts, Genetic Susceptibility, and Cancer Risk

The complex nature of the carcinogenic process challenges the molecular epidemiologist in determining cancer risk. It is hoped that by measuring multiple intermediate biomarkers of cancer risk that a specific inheritable susceptibility may be shown. There are several examples in the literature of studies that used a multidisciplinary approach of looking at the relationship between metabolic phenotypes/genotypes and biomarkers of exposure and cancer risk. For example, a case-control study by Bartsch *et al.* (109) demonstrated a correlation between *CYP1A1* expression in the lung and pulmonary polycyclic aromatic-DNA (PAH-DNA) adduct levels in tobacco smokers. This work and that of others (49, 110) implicate the role of *CYP1A1* in PAH metabolism by the human lung and suggest a rationale for the observed correlation of high *CYP1A1* expression and lung cancer risk in smokers. In a similar study, no correlation was found between the *CYP1A1* exon 7 mutation and PAH-DNA adducts in the lung tissue of smokers (111). Although, in this same study, increased adduct levels in parenchyma lung tissue were found to be associated with the null *GSTM1* genotype. Other studies of the *CYP1A1* phenotype instead of genotype, have observed a correlation between lung PAH-DNA adducts and *CYP1A1* activity among smokers (110, 112).

A recent study examined the relationship of *CYP2E1*, *CYP2D6*, *CYP1A1*, and *GSTM1* genetic polymorphisms with 7-methyl-2′-deoxyguanosine (7-methyl-dGp), 7-ethyl-2′-deoxyguanosine (7-ethyl-dGp), and polycyclic aromatic hydrocarbon-2′-deoxyguanosine (PAH-dGp) adducts in human lung tissues (100). An association was found between 7-methyl-dGp adduct levels and *CYP2E1* and *CYP2D6* genotypes, and also between PAH-dGp adducts and the *GSTM1* null genotype (100). The effects were greater in persons with lower cotinine levels, suggesting an interaction of genotype and environment. A case-control study looking at PAH-DNA adducts in white blood cells found that the *GSTM1* null genotype and adduct levels were independent risk factors for lung cancer (4, 113). An additional study of the *GSTM1* null genotype revealed about 3-fold more mutagens in urine of smokers with this genotype than in smokers with the full-length gene (114). This observation supports previous studies that reported increased risk for bladder cancer in persons containing the *GSTM1* null genotype (95).

Several studies of *NAT2* have reported higher levels of 4-ABP-hemoglobin adducts in persons with the slow acetylation genotype/phenotype compared with adduct levels of rapid acetylators (85, 115, 116). It was originally shown that phenotypically slow acetylators had more 4-aminobiphenyl-hemoglobin adducts, which correlated with an increased level of cigarette smoking (177). After taking into account indicators of cigarette smoking level (urinary nicotine and cotinine), further analysis suggested that persons with passive tobacco smoke exposure who were slow acetylators were at a greater risk of forming adducts compared to active tobacco smokers (115). In contrast to *N*-acetylation by *NAT2*, *O*-acetylation by *NAT1* appears to be involved in bioactivation of aromatic amines, and a recent study showed a correlation among the *NAT1**10 allele polymorphism,

higher *NAT1* (*O*-acetylation) activity, and elevated aromatic amine-DNA adducts (88).

Perspectives

The risk assessment process plays a vital role in the regulation of carcinogen exposure. Biologically based risk assessments will need to consider cancer as a multistep process, where the number of steps are not fully determined, but most likely more than previously demonstrated. Therefore, the use of multiple biomarkers and corroborative methods are required in order to detect risk factors which may be buried under a high background of other factors. In addition, interindividual variation in response to xenobiotics is an important concept in molecular epidemiology, which seeks to identify sensitive or resistant populations (family, ethnicity, and race) for more accurate risk assessment.

Methodological improvements have had a great impact on the rapid advancement of molecular epidemiology. PCR coupled with direct sequencing for mutation detection as well as the application of PCR for polymorphism analysis continues to aid in the identification of genes associated with cancer risk. In addition, there has been a recent surge of scientific studies on DNA microchip technology (118) for a variety of genetic analysis applications, which may have a significant impact on the mutational analysis of *p53* and cancer diagnosis (119). The identification of inherited and acquired host susceptibility factors is progressing at a rapid pace. In addition, quantitative methods to measure human exposures to carcinogens continue to improve, not only in sensitivity but also in specificity. Although several sensitive techniques have been developed to detect DNA damage, improvements are continually needed in order to decrease their labor intensiveness, cost, and intra- and interlaboratory variability, which is required in order to increase their applicability to large studies. Further room for growth involves the development of methods to measure multiple adducts simultaneously, which would be not only cost-effective, but also useful when investigators are faced with limited quantities of biological materials.

As the field of molecular epidemiology advances, several ethical issues need to be resolved in a societal and public health context. The potential interpretation and use of these assays in the workplace or general medical clinic has and will continue to generate significant controversy, including the possibility of discrimination based upon genotype. Society will need to determine in the near future the limits for use in the public sector and medical clinics. The potential benefits, however, of such risk assessment studies are clear. Measurement of biomarkers, such as the detection of high adduct levels, could aid in the identification of sensitive individuals or groups, which would allow the focusing of further studies. In addition, upon identification of such individuals, various strategies could be implemented to increase surveillance, increase preventative measures to limit or remove exposure, and/or chemopreventative measures could be employed.

It is hoped that, in the future, molecular epidemiologists will be able to develop a profile for an individual that includes assessment of multiple DNA damage (adducts and mutations), genotyping of metabolism, DNA repair, and susceptibilities based on germ line and altered proto-oncogenes and tumor suppressor genes. Multiple rigorous, multidisciplinary and corroborative studies will be required to accomplish this goal. Although considerable progress has been made in the molecular epidemiology of human cancer risk, more progress is needed. The field has the potential to have a significant impact on the quality of quantitative risk assessment, which may aid in the regulation of allowable exposures and in the identification of individuals who will most benefit by cancer prevention strategies.

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