Human DNA Adduct Measurements: State of the Art

Miriam C. Poirier[1] and Ainsley Weston[2]

[1]Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland; [2]Department of Community Medicine, Mount Sinai School of Medicine, New York, New York

Human DNA adduct formation (covalent modification of DNA with chemical carcinogens) is a promising biomarker for elucidating the molecular epidemiology of cancer. Classes of compounds for which human DNA adducts have been observed include polycyclic aromatic hydrocarbons (PAHs), nitrosamines, mycotoxins, aromatic amines, heterocyclic amines, ultraviolet light, and alkylating cancer chemotherapeutic agents. Most human DNA adduct exposure monitoring has been performed with either ^{32}P-postlabeling or immunoassays, neither of which is able to chemically characterize specific DNA adducts. Recently developed combinations of methods with chemical and physical end points have allowed identification of specific adducts in human tissues. Studies are presented that demonstrate that high ambient levels of benzo[*a*]pyrene are associated with high levels of DNA adducts in human blood cell DNA and that the same DNA adduct levels drop when the ambient PAH levels decrease significantly. DNA adduct dosimetry, which has been achieved with some dietary carcinogens and cancer chemotherapeutic agents, is described, as well as studies correlating DNA adducts with other biomarkers. It is likely that some toxic, noncarcinogenic compounds may have genotoxic effects, including oxidative damage, and that adverse health outcomes other than cancer may be correlated with DNA adduct formation. The studies presented here may serve as useful prototypes for exploration of other toxicological end points. — Environ Health Perspect 104(Suppl 5):883–893 (1996)

Key words: polycyclic aromatic hydrocarbons, occupational exposure, ambient benzo[*a*]pyrene, enzyme-linked immunosorbent assay, ^{32}P-postlabeling, fluorescence spectroscopy, gas chromatography–mass spectrometry, biomarkers

Introduction

A large body of evidence in experimental systems suggests that DNA adduct formation is necessary, but not sufficient, for tumorigenesis caused by genotoxic chemical carcinogens (*1,2*). Thus, human DNA adduct formation (covalent modification of DNA with chemical carcinogens) is a promising biomarker for elucidating the molecular epidemiology of cancer (*3,4*). Classes of compounds for which human DNA adducts have been measured include polycyclic aromatic hydrocarbons (PAHs), nitrosamines, mycotoxins, aromatic amines, heterocyclic amines, ultraviolet (UV) light and alkylating cancer chemotherapeutic agents. Human exposures that result in DNA adduct formation are listed in Tables 1 and 2, and some chemical structures of DNA adducts are shown in Figure 1. It is generally considered that DNA adduct formation represents biologically effective dose, or dose reaching a target tissue, and it is assumed that DNA adduct measurements have the potential to become integral components of the risk-assessment process. At the present time many technological approaches have sufficient sensitivity to measure human DNA adducts and are being used widely for exposure assessment. The advancement of the field to DNA adduct-based cancer risk assessment requires the implementation of adduct measurements within epidemiologically sound study designs, an area that is still in the early stages of development. It is also possible that toxic, but noncarcinogenic, compounds form DNA adducts and may have other adverse health outcomes for which DNA adduct formation may therefore be an appropriate biomarker.

Methods that have been used for sensitive detection of carcinogen–DNA adducts in humans include immunoassays (*5*), immunohistochemistry (*6,7*), ^{32}P-postlabeling, (*8,9*), fluorescence and phosphorescence spectroscopy (*10*), gas chromatography–mass spectrometry (GC–MS) (*11*), atomic absorbance spectrometry (AAS) (*12,13*) and electrochemical conductance (ECC) (*14*). Typically, the techniques that are used without preparative procedures are not absolutely quantitative or able to chemically characterize a specific adduct, but they are highly effective screening tools. Recent advances combining preparative methods [immunoaffinity chromatography (IAC), high performance liquid chromatography (HPLC) or other chromatography] with immunoassays, ^{32}P-postlabeling, synchronous fluorescence spectrometry (SFS), and GC–MS have allowed identification and quantitation of specific DNA adducts in human tissues potentially resulting in more precise exposure documentation.

This paper is an overview of methodologies and their application in exposure biomonitoring, focusing on human blood cell PAH–DNA adduct measurements obtained concomitantly with ambient PAH monitoring. DNA adduct dosimetry and correlation of DNA adducts with other biomarkers are considered.

This paper was presented at the Conference on Air Toxics: Biomarkers in Environmental Applications held 27–28 April 1995 in Houston, Texas. Manuscript received 24 May 1996; manuscript accepted 5 June 1996.

Address correspondence to Dr. M.C. Poirier, National Cancer Institute, Building 37, Room 3B25, National Institutes of Health, Bethesda, MD 20892. Telephone: (301) 402-1835. Fax: (301) 496-8709. E-mail: poirierm@dc37a.nci.nih.gov

Abbreviations used: AHH, aryl hydrocarbon hydroxylase; 3me- or 3et-Ade, 3-methyl- or 3-ethyladenine; 3OHet-Ade, 3-hydroxyethyladenine; 3bz-Ade, 3-benzyladenine; AFB_1, aflatoxin B_1; AFB_1-N^7-dG, aflatoxin B_1-N^7-deoxyguanosine; AAS, atomic absorbance spectrometry; B[*a*]P, benzo[*a*]pyrene; BPDE, *r*-7,*t*-8-dihydroxy-*c*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene; BPdG, (7R)-N^2-[10-[*r*-7, *t*-8, *t*-9-trihydroxy-7,8,9,10-tetrahydrobenzo[*a*]-pyrenelyl]-deoxyguanosine; BP-7,10/8,9-tetrol, *r*-7,*t*-8,*t*-9,*c*-10-tetrahydroxy-7,8,9,10-tetrahydro-benzo[*a*]pyrene; carboplatin, diamminecyclobutanedicarboxylatoplatinum (II); cisplatin, cis-diamminedichloroplatinum (II); dG-C8-4-ABP, *N*-deoxyguanosin-(8-yl)-4-aminobiphenyl; ECC, electrochemical conductance; ELISA, enzyme-linked immunosorbent assay; GC–MS, gas chromatography–mass spectrometry; HPLC, high performance liquid chromatography; 8OH-dG, 8-hydroxydeoxyguanosine; IAC, immunoaffinity chromatography; MOCA, 4,4′-methylene-bis(2-chloroaniline); N7OHet-dG, N7-hydroxyethyldeoxyguanosine; N7me- or N7et-dG, N7-methyl- or N7-ethyldeoxyguanosine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; O^6me- or O^6et-dG, O^6-methyl- or ethyldeoxyguanosine; O^4me - or O^4et-dT, O^4-methyl- or ethylthymidine; PAHs, polycyclic aromatic hydrocarbons; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; RIA, radioimmunoassay; SFS, synchronous fluorescence spectrometry; TLC, thin layer chromatography; UV, ultraviolet.

Table 1. Sensitivities and exposures measured for human DNA adduct detection using antisera specific for DNA adducts or modified DNA samples.

Assay	Adducts detected per 10^8 nucleotides	Exposure	Reference
Immunoassay	≥ 1	Aflatoxins	(*27–29*)
		4-Aminobiphenyl	(*30,31,130*)
		Cisplatin and carboplatin	(*38,85,116,131*)
		Coal tar (medicinal)	(*41*)
		Dacarbazine	(*40*)
		8-Methoxypsoralen	(*42*)
		Oxidative damage	(*43*)
		PAHs	(*35–37,108,132*)
		Procarbazine[a]	(*39,117*)
		Ultraviolet light	(*44*)
Immunohistochemistry	≥ 100	Aflatoxins	(*7*)
		Cisplatin	(*6,45*)
		8-Methoxypsoralen	(*46,47*)
		Ultraviolet light	(*48*)

[a]Competitive repair assay, analogous to immunoassay.

Table 2. Sensitivities and exposures measured for human DNA adduct detection by ^{32}P-postlabeling and other assays.

Assay	Adducts detected per 10^8 nucleotides	Exposure	Reference
^{32}P-Postlabeling	0.1	Coal tar (medicinal)	(*133*)
		Mitomycin C	(*134*)
		MOCA	(*135*)
		Ochratoxin A	(*136*)
		PAHs	(*9,55,105,109, 137–139*)
		Styrene	(*140–142*)
		Tobacco	(*143–145*)
		Unknown	(*36,146–149*)
Luminescence spectroscopy	10–100	Aflatoxins	(*63,150*)
		B[*a*]P	(*61,67,151*)
		PAH (occupational)	(*65,66*)
GC–MS	0.3–1	4-Aminobiphenyl	(*83*)
		N-Nitrosamines	(*11,73,77,78,80*)
		NNK (tobacco)	(*81*)
		PhIP (diet)	(*84*)
		Malondialdehyde (endogenous)	(*152*)
Atomic absoprtion spectrometry	100	Cisplatin and carboplatin	(*86,153*)
Electrochemical conductance	0.1–1[a]	Oxidative damage	(*93,94*)

[a]Picomole per milliliter of urine.

Major Methods for DNA Adduct Determination in Human Tissues and Examples of Human Exposure Monitoring

Immunoassays

Antisera elicited against DNA adducts and carcinogen-modified DNA samples (*15–17*) have been widely used to quantify and localize xenobiotic-induced DNA damage (*18–21*) and to measure DNA adduct formation in human tissues (*22,23*). Competitive radioimmunoassays (RIAs) and enzyme-linked immunosorbent assays (ELISAs), able to detect human DNA damage with sensitivity in the range of one adduct in 10^8 unmodified nucleotides, have been established with these antisera. Immunoassays are reliable, inexpensive, and allow for the analysis of more than 20 samples per day. Disadvantages include the requirement for relatively large amounts of DNA (200 µg) and a lack of absolute specificity because of antibody cross-reactivity. Cross-reactivity with unmodified DNA, unmodified nucleotides, or carcinogen alone rarely occurs (*24*), but there may be recognition of other adducts of the same carcinogen or adducts of other chemically related compounds (*25*). Therefore, unless prior separation of adducts is used, the values obtained for human samples may reflect measurement of multiple, chemically similar DNA adducts. In addition to use with quantitative immunoassays, anticarcinogen DNA adduct antisera have been used for immunohistochemical staining of human tissues (*21,23,26*). In general, immunohistochemistry is less sensitive than ELISA, but the approach may be relevant for identification of susceptible cell types in complex tissues.

Xenobiotic exposures that have been examined by immunoassay in samples from human subjects (Table 1) include aflatoxins (*27–29*), 4-aminobiphenyl (*30,31*), *N*-nitrosamines (*32–34*), benzo[*a*]pyrene (B[*a*]P), and other PAHs (*35–37*). In addition, medicinal exposures, including *cis*-diamminedichloroplatinum (II) (cisplatin) (*38*), procarbazine (*39*), dacarbazine (*40*), coal tar (*41*), and 8-methoxypsoralen (*42*) have been determined in DNA of patients. Oxidative DNA damage (*43*) and UV light photoproducts (*44*) have also been measured by immunoassay. Immunohistochemistry to localize DNA adducts in human tissues (Table 1) has been used for aflatoxins (*7*), cisplatin (*6,45*), 8-methoxypsoralen (*46,47*), and UV light (*48*).

^{32}P-Postlabeling

The ^{32}P-postlabeling technique is widely used for human DNA adduct detection (*9,20,23*), largely because of its high sensitivity (routinely one adduct in 10^9 nucleotides) and application to small quantities of DNA (2–10 µg). The method is based on the radiolabeling of adducts with high specific activity ^{32}P from γ^{32}P-ATP by T4 polynucleotide kinase. DNA isolated from a tissue of interest is digested to 3′-monophosphates and phosphorylated to form 5′-^{32}P-3′-bisphosphates. Adducts in the labeled mixture are separated by thin layer chromatography (TLC) in multiple (most often four) directions. Relative quantitation has been approached by scraping materials from the TLC plates and subjecting them to radiochemical analysis; however, recent development of a sensitive radiomatic apparatus for chromatogram scanning facilitates the quantitation and provides a measure of protection for laboratory personnel. Advantages and disadvantages of this method have been discussed in detail elsewhere (*23,49*).

Individuals receiving many different types of potentially genotoxic exposures have been demonstrated to have potential adduct spots by ^{32}P-postlabeling (Table 2), and in the absence of other information

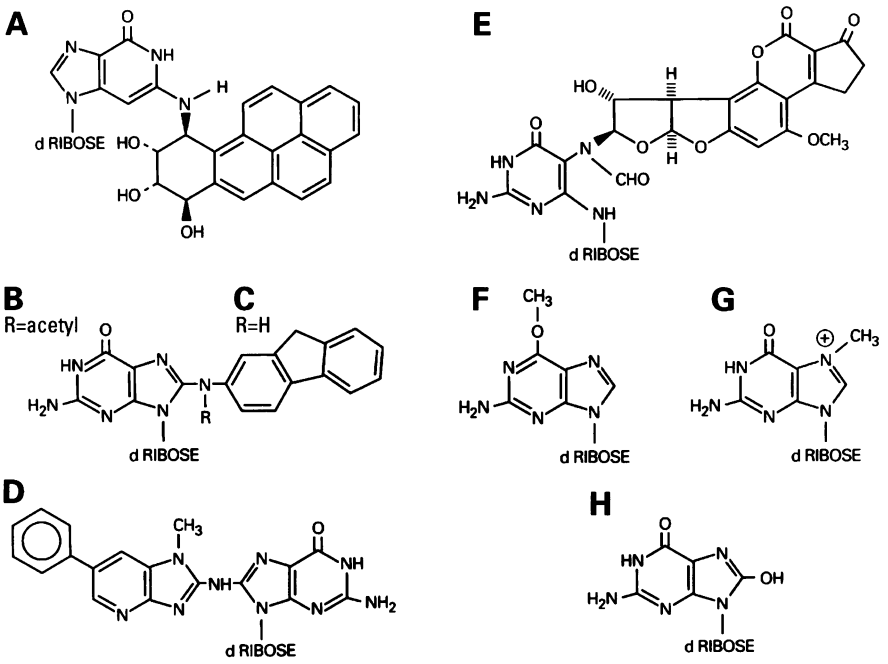

Figure 1. Structures of representative DNA adducts. (*A*) (7*R*)-N^2-{10-[*r*-7, *t*-8, *t*-9-trihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene]yl}-deoxyguanosine; (*B*) *N*-deoxyguanosin-(8-yl)-2-acetylaminofluorene; (*C*) *N*-deoxyguanosin-(8-yl)-2-aminofluorene; (*D*) N2-(2′-dG-8-yl)-2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; (*E*) aflatoxin B_1-N7-deoxyguanosine; (*F*) O^6-methyldeoxyguanosine; (*G*) N7-methyldeoxyguanosine; (*H*) 8-hydroxydeoxyguanosine.

these are termed "aromatic adducts." The chemical identification of such adducts has rarely been achieved, but recent sophisticated modifications to the basic methodology have allowed tentative identification of some specific adducts (*30,50,51*). Overall, correlations of adduct levels with documented human exposure appear to be good (*52–56*), but the quantitative data should be interpreted with caution because the adducts are unidentified and the efficiency of phosphorylation is often unknown and uncontrolled (*51,57–60*).

Luminescence and Phosphorescence Spectroscopy

Luminescence spectroscopy is possible only with carcinogens having intrinsic fluorescence, such as PAHs and aflatoxins. In SFS, both the excitation and emission monochromators are driven simultaneously at a distance equal to the Stoke's shift so that a fluorescence signal is observed when the last excitation maximum and first emission maxima are met. This approach simplifies the spectrum and allows for the generation of more complete fluorescence excitation–emission matrices (*61–63*). Conventional SFS detection of (7*R*)-N^2-{10-[*r*-7,*t*-8,*t*-9- trihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene]yl}-deoxyguanosine (BPdG) in human tissues requires acid hydrolysis (0.1 N HCl, 90°C, 3 hr) of the DNA and isolation of the B[*a*]P residues as *r*-7,*t*-8,*t*-9,*c*-10-tetrahydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene, (BP-7,10/8,9-tetrol). A detection limit of one adduct in 10^6 to 10^7 unmodified nucleotides has been achieved for 100 µg of DNA (*64–66*).

A recently developed approach involves the use of analytical solid matrix phosphorescence spectroscopy to detect BP-7,10/8,9-tetrol. The method uses a solid matrix composed of hydrophobic cyclodextrins to adsorb PAH residues followed by laser excitation (*67*), and the limit of detection is 20 to 50 times lower than conventional SFS.

The major limitations to the use of fluorescence spectroscopy for the detection of carcinogen DNA damage in humans are lack of prior knowledge of adduct chemistry, a requirement that the adduct be fluorescent, and a requirement for relatively large quantities of sample DNA (100–1000 µg). After the initial cost of the equipment, assays can be performed rapidly and inexpensively. To date (Table 2), fluorescence studies have been restricted to detection of DNA adducts containing a pyrene fluorophore (*49,68*), detection of exfoliated aflatoxin adducts in urine (*69*), and *N*7-methyl-deoxyguanosine (N7me-dG) and O^6-methyl-deoxyguanosine (O^6me-dG) adducts in liver in a case of acute poisoning (*70*).

Gas Chromatography–Mass Spectrometry

Gas chromatography–mass spectrometry (*49,71*) is highly specific and has had widespread application in measurement of both carcinogen–protein adducts and carcinogen–DNA adducts (*72–76*). Mass spectrometry requires derivitization of the compound of interest to increase mass and volatility; vaporization of the sample; ionization, which can be achieved in a number of ways (electron impact, fast atom bombardment, chemical ionization, and laser desorption); collimation of the charged particles; and acceleration into the mass analyzer. The spectrum of ions detected comprises the molecular ion plus the fragment ions including the base peak. The base peak, the most intense signal, is most commonly used for quantitative sample analysis by single-ion monitoring when the mass spectrum of a compound of interest is already known.

Methods using GC–MS have been developed for several different exposures (Table 2). Alkyl purine adducts in human urine have been the most extensively studied (*11,72,73,77–80*). These investigations have examined the exfoliation of adducts by seeking the presence of N7me-dG, N7et-dG, *N*7-hydroxethyldeoxyguanosine (N7-OHet-dG), 3-methyladenine (3me-Ade), 3-ethyladenine (3et-Ade), 3-hydroxyethyladenine (3OHet-Ade), and 3-benzyladenine (3bz-Ade) in human urine. Investigations using single-ion monitoring GC–MS have been extended to the measurement of 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) adducts in human lung and tracheal DNA of smokers and nonsmokers (*81*). In addition, the presence of BPdG has been demonstrated in placental tissues of smokers and nonsmokers (*82*). Samples of human urinary bladder and lung DNA, digested and subjected to negative ion GC-MS, were shown to contain *N*-deoxyguanosin-(8-yl)-4-aminobiphenyl (dG-C8-4-ABP) at levels that compared well with ^{32}P-postlabeling analysis of the same samples using appropriate standards (*83*). Similarly, the C-8 DNA adduct of the heterocyclic amine 2-amino-1-methyl-6-phenylimidazo-[4,5-*b*]pyridine (PhIP) was observed by GC–MS after hydrolysis from human colon (*84*).

Atomic Absorbance Spectrometry

Atomic absorbance spectrometry is an analytical method for determining elements based on the absorbance of radiation by free atoms released by high-temperature combustion. It is most valuable in the detection of metal ions and has been successfully applied, for human dosimetry, in the monitoring of DNA from cancer patients treated with the platinum drugs, cisplatin and diamminecyclobutane-dicarboxylatoplatinum (II) (carboplatin) (Table 2). These drugs have been shown by AAS (*12*) and other methods to bind covalently to DNA (*45,85–87*). For measurement of platinum bound to DNA in tissues of human cancer patients, unknown samples are quantified by comparison to a standard curve, and sufficient sensitivity is only obtained using an AAS with Zeeman background correction (*86,88*).

Electrochemical Conductance

Electrochemical conductance requires the application of a voltage across two electrodes that are immersed in an electrolytic solution. An electric current flows, allowing the measurement of electrical conductance, which is proportional to the analyte concentration (*89*). This technique has the advantage of specificity because it can be directly applied to individual HPLC fractions (*14*). However, factors related to the chromatographic conditions (gradient elution, temperature, and pressure) may cause problems with detector performance (*90,91*).

Electrochemical conductance has been used to monitor oxidative damage in DNA (Table 2). This use of the method is complicated by the fact that oxidation of DNA may occur during the extraction procedure (*92*); however, 8-hydroxydeoxyguanosine (8OH-dG) is detectable, whereas unmodified deoxyguanosine is not. The approach is sufficiently specific and sensitive for human biomonitoring, but investigations so far have been limited to determining 8OH-dG in urine, peripheral white blood cells, or bronchial alveolar macrophages (*93,94*).

Combinations of Methods

The most frequently applied detection methods, immunoassays, ^{32}P-postlabeling, and fluorescence spectroscopy, used in the absence of micropreparative techniques, provide a broad screen and indicate exposure. However, recently devised combinations of methods produce more specific and readily comprehensible data. Such approaches are necessarily more labor intensive, time consuming, expensive, and demanding when applied to large numbers of specimens, but the information they provide is invaluable for human exposure assessment.

Most combinations of methods to improve the specificity of DNA adduct detection use either conventional chromatographic separation or immunoaffinity chromatography as a first step. When a human DNA sample is digested and subjected to HPLC, even though the adducts cannot be observed by conventional monitoring, the fractions known to contain specific adducts can be analyzed by immunoassay, ^{32}P-postlabeling, or GC–MS. For example, the sensitivity and specificity of ELISAs for human DNA adduct monitoring have been enhanced by combination with prior HPLC. This approach has been applied to human gastric mucosa (*32*) and liver samples (*33*) using antisera specific for alkyl-modified nucleosides. Chromatographic separation by HPLC has also been combined with ^{32}P-postlabeling; a recent review (*59*) covers the subject. A highly successful line of experimentation has combined two chromatographic steps with ^{32}P-postlabeling to detect specific O^6- and N7-alkyl-dG adducts in human lung and lymphocytes (*51,57,95*). The development of this method has facilitated the use of internal and cochromatography standards. In an another approach, Stillwell et al. (*79*) employed two chromatographic steps prior to the GC–MS determination of 3me-dA and 7me-dG adducts in the urine of smokers. Finally, in a novel set of experiments, HPLC was used as the first step of a procedure combining ^{32}P-postlabeling with immunoprecipitation (termed PREPI) for the detection of O^{6}me-dG, O^{4}me-dG, and O^{4}et-dG in human liver and leukocyte DNA samples (*50*).

Immunoaffinity chromatography provides a valuable purification step that has been widely used to improve the specificity of other methods. Antibodies elicited against DNA adducts or carcinogen-modified DNA samples can be covalently bound to a matrix and the resulting material used in columns that bind and elute specific adducts in a DNA digest. Because most antisera have cross-reactivity for families of structurally similar DNA adducts, IAC concentrates structurally similar DNA adducts (*96–98*). Further separation of adducts by HPLC is frequently required before specific adduct determination is possible.

For PAH exposure, IAC and HPLC of human lung and placenta have been combined with different end points, including SFS (*82,98,99*), GC–MS (*82*), and ^{32}P-postlabeling (*99,100*), to provide evidence of BPdG formation. Using this methodology, it is possible to detect one BPdG adduct in 10^8 nucleotides.

Immunoaffinity chromatography and GC–MS have been combined to detect exfoliated 3-alkyl-adenines in human urine (*11,80*). Recently, Bianchini et al. (*101*) reported the combination of IAC, HPLC, and ECC to measure N7me-dG in human pancreas. Aflatoxin exposure dosimetry has been accomplished by combining IAC with HPLC and UV absorbance (A_{362}) to detect adducts in human urine and tissues (*28,102,103*). In other studies IAC has been combined with ^{32}P-postlabeling and TLC to detect O^6 me-dG (*104*).

Human DNA Adduct Formation as an Exposure Dosimeter

Comparison of Ambient B[*a*]P Levels with DNA Adduct Formation

A number of investigatiors have attempted to monitor ambient air for B[*a*]P and other PAHs while simultaneously measuring blood cell DNA adducts in occupationally or environmentally exposed individuals. Studies focused only on smoking have been excluded here because the dosimetry is necessarily crude, and PAH–DNA adduct levels in blood-cell DNA are not consistently higher in smokers. In fact, the results suggest that smoking is only one of many factors that contribute to adduct formation in blood cell DNA. This analysis focuses on adduct measurements in human blood-cell DNA because human tissue biopsies are not practical for routine analysis.

A summary of investigations in which ambient B[*a*]P levels were compared to PAH–DNA adduct analyses in human blood cells is shown in Table 3. Overall, the data suggest that increased ambient pollution levels (using B[*a*]P as an indicator) are associated with higher levels of blood-cell PAH–DNA adducts, and that measures taken to remove B[*a*]P (and presumably other PAHs) from the environment yield dividends in terms of lowered biologically effective dose. Two studies in a population of Finnish foundry workers, performed several years apart, indicate that decreasing the B[*a*]P levels from 12–200 ng/m^3 to < 5–60 ng/m^3 significantly reduced the PAH–DNA adduct levels measured by the anti-BPdG–DNA–ELISA (*37,41*). In addition, lower

Table 3. Human white blood-cell DNA adduct levels (adducts/10^8 nucleotides) as a function of ambient benzo[*a*]pyrene (ng/m^3) levels.

Cohort	<1 ng/m^3	< 5 ng/m^3	5–12 ng/m^3	12–60 ng/m^3	50–50,000 ng/m^3	Assay	Reference
Finnish foundry	2.2[a]			8.0	21.0, 50.0	ELISA	(*37*)
Finnish foundry		5.2	6.1	9.6		ELISA	(*41*)
Dutch coke ovens	2.8[a]				5.2	ELISA	(*109*)
Polish coke ovens				8.2	24.5	^{32}P-Postlabeling	(*110*)
				2.3	15.3	ELISA	
Silesia, Poland		1.3 (summer)[b]		6.4 (winter)[b]		^{32}P-Postlabeling	(*107*)
U.S. Army soldiers	1.6 (Kuwait)		4.0 (Germany)			DELFIA	(*106*)
	1.7 (Kuwait)		3.0 (Germany)			^{32}P-Postlabeling	
Chinese women				9.2 (methane)[c]	3.3 (smoky coal)[c]	ELISA	(*108*)

For comparison, ambient B[*a*]P levels from cigarette smoking are 2.8 to 760 ng/m^3 (*154*). [a]Controls. Ambient monitoring was typically not conducted for individuals serving as controls. [b]DNA adduct values are for lymphocytes only. [c]Of the methane controls, 4/16 (25%) were positive; for samples from coal smoke, 17/30 (57%) were positive.

PAH–DNA adduct levels were measured in the same workers after time spent on vacation (*105*).

In a study of U.S. Army soldiers, military personnel were monitored before, during, and after a tour of duty in Kuwait (*106*). It was expected that higher exposure to PAHs would result from oil-well fires burning at that time. However, the DNA adduct and air sampling data indicate that these soldiers went from a clean environment in Kuwait in August to significantly higher pollution levels in Germany in October, and DNA adducts, assayed by both BPdG–DNA dissociation-enhanced lanhtanide fluoroimmunoassay and ^{32}P-postlabeling, increased significantly (*106*).

Another example of pollution modulation and concomitant reduction in DNA adduct levels occurred in the Silesian region of Poland in the summertime; the air was approximately 5-fold cleaner than in the winter, and the levels of adducts in lymphocytes was approximately 5-fold lower (*107*). One should note, however, that the adduct dosimetry shown here to reflect ambient PAH levels is not consistent with the much higher levels of ambient B[*a*]P and the disproportionately low adduct levels observed in other studies (Table 3).

Of all the studies summarized in Table 3, the highest reported ambient B[*a*]P levels were 2283 ng/m^3 for Chinese women breathing coal smoke (*108*), 7800 ng/m^3 for Dutch coke oven workers (*109*), and 50,000 ng/m^3 for Polish coke oven workers (*110*). Of these, neither Dutch coke oven workers nor Chinese women had proportionately higher DNA adduct levels. The Chinese women, who have a high lung cancer risk, were exposed to coal smoke while cooking meals (*108*), but the Dutch workers experienced 100 to 7800 ng/m^3 during a 40-hr week (109). Therefore, in analyzing these data, a number of confounding factors must be recognized. The use of ambient B[*a*]P measurements provide an indicator of the pollution levels, but the actual hydrocarbon components vary and are not always measured. The BPdG-DNA immunoassays used actually measure BPdG as well as a broad spectrum of PAH–DNA adducts, since the antiserum used in many studies (*96,111,112*) recognizes multiple PAH–DNA adducts (*98*). In addition, cohorts are grouped according to the highest exposure documented, but the range of exposures for one job at one work site can vary considerably. Overall, the data suggest that DNA adduct levels vary with pollution, and that B[*a*]P may not be the compound responsible for producing the majority of PAH–DNA adducts observed by immunoassay and ^{32}P-postlabeling in human blood cells.

DNA Adduct Dosimetry

As discussed above, because much of the available human DNA adduct dosimetry for occupational and environmental exposures depends on ambient biomonitoring, precise dose–response relationships have not been possible. However, in some studies with dietary carcinogen exposure and others involving DNA-damaging cancer chemotherapeutic agents, dosimetry has been demonstrated.

In one study involving California firefighters (*113*), blood samples were taken before the summer firefighting season began and 8 weeks later. PAH–DNA adducts were measured by BPdG-DNA ELISA and did not correlate with the extent of firefighting. Comparison of questionnaire results with DNA adduct values showed that individuals (n = 19) consuming charbroiled food one to two times in the previous week had a mean PAH–DNA adduct value of 1.6 adducts in 10^8 nucleotides. Twenty-three individuals who reported consumption of these foods three to five times in the previous week and five individuals reporting consumption more than five times in the previous week had mean adduct values of 3.0 and 6.7 adducts/10^8 nucleotides, respectively. The largest single source responsible for PAH–DNA adduct formation was consumption of charbroiled food.

For dosimetry of aflatoxin exposure, 42 individuals in the Guangxi region of China were studied (*103*). Samples of the food consumed were assayed for aflatoxin content, which was correlated with the urinary excretion of aflatoxin-N^7-guanine (AFB_1-N^7-G) by both males and females. Immunoaffinity chromatography and HPLC were used to isolate metabolites and adducts from urine (*28,114*) and fluorescence emission spectra were used to identify the AFB_1-N^7-G. The dosimetry data showed an excellent correlation between dietary aflatoxin intake and urinary adduct excretion (*69*).

Cancer chemotherapy has presented unique opportunities to demonstrate DNA adduct dosimetry because the doses of drug are precisely known. Analysis of blood-cell DNA from 77 previously untreated ovarian and testicular cancer patients receiving platinum drug-based therapy showed strong DNA adduct dosimetry in patients with measurable DNA adduct levels (*115,116*). In studies with procarbazine and dacarbazine, which were used to treat patients with Hodgkin's lymphoma, an excellent correlation was shown between cumulative drug dose and blood-cell DNA levels of the O^6me-dG adduct (*39,117*). In general, the presence of high levels of DNA adducts appears to correlate positively with favorable clinical outcome (*118*), and therefore such analyses may become important clinical dosimeters. In addition, they serve to validate the assays commonly used for human DNA adduct measurements, since precise dosimetry is rarely possible in a clinical setting.

Correlation of DNA Adducts with Other Biomarkers

The classes of biomarkers most likely to correlate with PAH–DNA adduct measurements are urinary metabolites (biomarkers of exposure), hemoglobin adducts (surrogates for DNA adducts), mutagenesis (biomarkers of effect), and polymorphisms for enzymes involved in PAH metabolism (biomarkers of susceptibility). Studies currently available in this area have been performed with small numbers of subjects, and conflicting correlations have sometimes been observed. However, as methodological advances improve the specificity of biomarker analysis, there is the promise that batteries of such assays may be usefully employed in future risk assessments.

Metabolic polymorphisms are considered to influence all the other classes of biomarkers. The enzyme complex responsible for the initial metabolism of PAHs, aryl hydrocarbon hydroxylase (AHH), consists of a battery of enzymes that include cytochrome P4501A1. The extent of AHH activity in human lung microsomes has been compared to DNA adduct levels determined in the same lung samples by either HPLC and fluorescence (specific for BPdG) (*119*) or ^{32}P-postlabeling (*53*). Both DNA adduct detection methods yielded results that correlated positively with the extent of AHH activity. Correlations of blood-cell DNA adduct levels with CYP1A1 have been examined in chimney sweeps (*155*) and in California firefighters (*156*) with ambivalent results. The lack of agreement may be due to differences in experimental approaches to determining polymorphism and to detecting DNA adducts, but it is also possible that neither study had sufficient statistical power to demonstrate subtle effects.

Another metabolic enzyme class, the glutathione *S*-transferases (GSTs), is involved in PAH detoxification. An 8-kb deletion, including the entire coding region of the *GSTM1* gene, renders the null genotype in approximately 45% of people who are homozygotes. This genotype has been implicated in increased aflatoxin–DNA adduct formation. To investigate PAH exposure levels in lung tissue, Shields et al. (*100*) showed that measurable BPdG adduct levels, by SFS and IAC/^{32}P-postlabeling, were present in six of seven people with the null genotype. Among individuals who were negative for these adducts, only 12 of 31 individuals had the null genotype. However, studies with blood-cell DNA adduct measurements did not show a similar correlation. For example, PAH–DNA adduct levels, measured by ELISA in blood cells from heavily smoking males with the null genotype (32/63) were similar to those found in matched individuals with homozygous or heterozygous normal genotypes (31/63) (*120*). In addition, in California firefighters who had significant increases in blood-cell PAH–DNA adducts due to eating charbroiled food, the presence or absence of the null genotype was not associated with consistent fluctuations in adduct levels (*156*). It is not likely that a single metabolic polymorphism will be the major determinant of cancer risk, but the results from a metabolic profile may be useful for future elucidation of susceptibility.

Urinary metabolites, hemoglobin adducts, and *HPRT* mutagenesis are being analyzed in conjunction with DNA adducts in human biomonitoring studies. Although few of these multiple biomarker studies are published, a number of promising new methodologies make this an important direction for the future. Urinary metabolites are considered to provide direct evidence of exposure and reflect the activity of the enzymes discussed above. The metabolite measured most frequently is 1-OH-pyrene (*121*), and the extent and timing of 1-OH-pyrene excretion have been correlated with occupational PAH exposures (*122*). In one study, PAH–DNA adducts and 1-OH-pyrene were measured in Finnish Foundry workers at three levels of ambient B[*a*]P exposure (*41*), and whereas adducts did correlate with exposure, the urinary metabolite did not. Subsequently, analytical procedures have been developed for the BP-7,10/8,9-tetrol (*123*) and the 1-OH-pyrene glucuronide (*124*), and these are now being measured in conjunction with DNA adducts (*106*). A number of methodological approaches for PAH analysis of human hemoglobin have demonstrated the presence of adducts derived from B[*a*]P and chrysene (*66,125,126*). Hemoglobin adducts of B[*a*]P were measured concomitantly with airborne PAH concentration in one study (*127*), and a weak correlation was demonstrated with exposure, but DNA adducts were not measured. Attempts have been made to correlate *HPRT* mutagenesis with exposure and DNA adduct formation in Finnish foundry workers (*128,129*). There was a significant increase in *HPRT* mutagenesis and DNA adduct formation with exposure, but the numbers of individuals in the mutagenesis portion of the study were small (*128*) and the correlation requires more substantial validation.

Taken together, these results demonstrate that multiple biomarker correlations are not necessarily straightforward. The tissues studied, the nature of the parameters being measured, and the capabilities of the assays used should all be carefully scrutinized. The numbers of subjects available may be insufficient for solid statistics, and the validity of a particular correlation may not be established until after several independent investigations are performed. However, the present status of development of several biomarkers suggests that good correlation studies with PAH–DNA adduct measurements can now be designed.

Conclusion

Human DNA adduct formation is a promising biomarker for molecular cancer epidemiology. The recent development of methodologies capable of measuring classes of adducts and specific adducts in human blood and tissue samples is likely to lead to improved risk assessment for groups of exposed individuals and may indicate opportunities for chemoprevention. This is true not only for cancer but for other toxic biological end points. Human DNA adduct measurements have been most widely used for exposure documentation. The studies presented here demonstrate that high ambient levels of B[*a*]P are associated with high levels of DNA adducts in human blood cell DNA and that DNA adduct levels drop when the ambient PAH levels decrease significantly. Precise human DNA adduct dosimetry has been difficult to achieve with PAHs because of the complex nature of the exposures involved; however, correlating DNA adducts with other exposure biomarkers such as urinary metabolites and hemoglobin adducts may substantiate ambient B[*a*]P measurements and approach dosimetry. Correlations with human mutagenesis and metabolic polymorphisms also suggest the importance of a battery of biomarkers in elucidating toxic mechanisms. It is likely that some toxic, noncarcinogenic compounds may have genotoxic effects and that adverse health outcomes other than cancer may be correlated with DNA adduct formation. Therefore, the studies presented here may serve as useful prototypes for exploration of other toxic end points.

REFERENCES

1. Yuspa SH, Poirier MC. Chemical carcinogenesis: from animal models to molecular models in one decade. Adv Cancer Res 50:25–70 (1988).
2. Beland FA, Poirier MC. DNA adducts and carcinogenesis. In: Pathobiology of Neoplasia (Sirica AE, ed). New York:Plenum Press, 1989;57–80.
3. Wogan GN. Markers of exposure to carcinogens. Environ Health Perspect 81:9–17 (1989).
4. Poirier MC, Beland FA. DNA adduct measurements and tumor incidence during chronic carcinogen exposure in animal models: implications for DNA adduct-based human cancer risk assessment. Chem Res Toxicol 5:749–755 (1992).
5. Poirier MC, Gupta-Burt S, Litterst CL, Reed E. Detection of cisplatin-DNA adducts in humans. In: Immunoassays for Monitoring Human Exposure to Toxic Chemicals. (Vanderlaan M, ed). Washington:American Chemical Society; 300–307.
6. Terheggen PM, Dijkman R, Begg AC, Dubbelman R, Floot BG, HartAA, den Engelse L. Monitoring of interaction products of *cis*-diamminedichloroplatinum(II) and *cis*-diammine(1,1-cyclobutane-dicarboxylato)platinum(II) with DNA in cells from platinum-treated cancer patients. Cancer Res 48:5597–5603 (1988).
7. Hsieh LL, Hsu SW, Chen DS, Santella RM. Immunological detection of aflatoxin B_1-DNA adducts formed *in vivo*. Cancer Res 48:6328–6331 (1988).
8. Reddy MV, Randerath KK. Nuclease P1-mediated enhancement of sensitivity of ^{32}P-postlabeling test for structurally diverse DNA adducts. Carcinogenesis 7:1543–1551 (1986).
9. Beach AC, Gupta RC. Human biomonitoring and the ^{32}P-postlabeling assay. Carcinogenesis 13:1053–1074 (1992).
10. Weston A, Bowman ED, Manchester DK, Harris CC. Fluorescence detection of lesions in DNA. In: DNA Damage and Repair in Human Tissues (Sutherland BM, Woodhead AD, eds). New York:Plenum Press; 1990;63–81.
11. Shuker DEG, Prevost V, Friesen MD, Lin D, Ohshima H, Bartsch H. Urinary markers for measuring exposure to endogenous and exogenous alkylating agents and precursors. Environ Health Perspect 99:33–37 (1993).
12. Reed E, Sauerhoff S, Poirier MC. Quantitation of platinum-DNA binding after therapeutic levels of drug exposure. Atomic Spectroscopy 9:93–95 (1988).
13. Reed E, Ozols RF, Tarone R, Yuspa SH, Poirier MC. The measurement of cisplatin-DNA adduct levels in testicular cancer patients. Carcinogenesis 9:1909–1911 (1988).
14. Floyd RA, Watson JJ, Wong PK, Altmiller DH, Rickard RC. Hydroxyl free radical adduct of deoxyguanosine: sensitive detection and mechanisms of formation. Free Radic Res Commun 1:63–172 (1993).
15. Poirier, MC. Antibodies to carcinogen-DNA adducts. J Natl Cancer Inst 67:515–519 (1981).
16. Poirier MC. The use of carcinogen-DNA adduct antisera for quantitation and localization of genomic damage in animal models and the human population. Environ Mol Mutagen 6:879–887 (1984).
17. Muller R, Rajewsky MF. Sensitive radiommunoassay for detection of O^6-ethyldeoxyguanosine in DNA exposed to the carcinogen ethylnitrosourea *in vivo* or *in vitro*. Z Naturforsch 33:897–901 (1978).
18. Leng M, Sage E, Fuchs RP, Duane MP. Antibodies to DNA modified by the carcinogen *N*-acetoxy-N^2-acetylaminofluorene. FEBS Lett 92:207–210 (1978).
19. Strickland PT, Boyle JM. Immunoassay of carcinogen-modified DNA. Prog Nucleic Acid Res Mol Biol 31:1–58 (1984).
20. Phillips DH. Modern methods of DNA adduct determination. In: Handbook of Experimental Pharmacology. Vol 94:I (Cooper CS, Grover PL, eds). Berlin:Springer-Verlag, 1990;503–546.
21. Santella RM, Yang XY, Hsieh LL, Young TL. Immunologic methods for the detection of carcinogen adducts in humans. Prog Clin Biol Res 340C:247–257 (1990).
22. Poirier MC, Yuspa SH, Weinstein IB, Blobstein S. Detection of carcinogen-DNA adducts by radioimmunoassay. Nature 270:186–188 (1977).
23. Poirier MC, Weston A. DNA adduct determination in humans. Prog Clin Biol Res 372:205–218 (1991).
24. Santella RM, Hsieh LL, Lin CD, Viet S, Weinstein IB. Quantitation of exposure to benzo[*a*]pyrene with monoclonal antibodies. Environ Health Perspect 62:95–99 (1985).
25. Poirier MC. Development of Immunoassays for the Detection of Carcinogen-DNA Adducts. In: Molecular Dosimetry and Human Cancer (Skipper PL, Groopman JD, eds). Boca Raton, FL:CRC Press 1991;211–229.
26. Poirier MC. Immunochemical methods for assaying carcinogen-DNA adducts. In: Human Carcinogen Exposure (Garner RC, Farmer PB, Steel GT, Wright AS, eds). Oxford:Oxford University Press, 1991;69–83.
27. Lee HS, Sarosi I, Vyas GN. Aflatoxin B_1 formamidopyrimidine adducts in human hepatocarcinogenesis: a preliminary report. Gastroenterology 97:1281–1287 (1989).
28. Groopman JD, Donahue PR, Zhu JQ, Chen JS, Wogan GN. Aflatoxin metabolism in humans: detection of metabolites and nucleic acid adducts in urine by affinity chromatography. Proc Natl Acad Sci USA 82:6492–6496 (1985).
29. Sun TT, Wu SM, Wu YY, Chu Y. Measurement of individual aflatoxin exposure among people having different risk to primary hepatocellular carcinoma. In: Diet, Nutrition and Cancer (Hyaishi Y, Nagao M, Sugimura T, Takayama S, Tomatis L, Wattenberg W,Wogan GN, eds). Tokyo:Japan Scientific Society Press 1986;225–235.
30. Talaska G, al-Juburi AZ, Kadlubar FF. Smoking related carcinogen-DNA adducts in biopsy samples of human urinary bladder: identification of *N*-(deoxyguanosin-8-yl)-4-aminobiphenyl as a major adduct. Proc Natl Acad Sci USA 88:5350–5354 (1991).
31. Roberts DW, Benson RW, Groopman JD, Flammang TJ, Nagle WA, Moss AJ, Kadlubar FF. Immunochemical quantitation of DNA adducts derived from the human bladder carcinogen 4-aminobiphenyl. Cancer Res 48:6336–6342 (1988).
32. Umbenhauer D, Wild CP, Montesano R, Saffhill R, Boyle JM, Huh N, Kirstein U, Thomale J, Rajewsky MF, Lu SH. O^6-Methyldeoxyguanosine in oesophageal DNA among individuals at high risk of oesophageal cancer. Int J Cancer 36: 661–665 (1985).
33. Huh NH, Satoh MS, Shiga J, Rajewsky MF, Kuroki T. Immunoanalytical detection of O^4-ethylthymine in liver DNA of individuals with or without malignant tumors. Cancer Res 49:93–97 (1989).
34. Kyrtopoulos SA, Ampatzi P, Davaris P, Haritopoulos N, Golematis B. Studies in gastric carcinogenesis. IV: O^6-Methylguanine and its repair in normal and atrophic biopsy specimens of human gastric mucosa. Correlation of O^6-alkylguanine-DNA alkyltransferase activities in gastric mucosa and circulating lymphocytes. Carcinogenesis 11:431–436 (1990).
35. Haugen A, Becher G, Benestad C, Vahakangas K, Trivers GE, Newman MJ, Harris CC. Determination of polycyclic aromatic hydrocarbons in the urine, benzo[*a*]pyrene diol epoxide-DNA adducts in lymphocyte DNA, and antibodies to the adducts in sera from coke oven workers exposed to measured amounts of polycyclic aromatic hydrocarbons in the work atmosphere. Cancer Res 46:4178–4183 (1986).
36. van Schooten FJ, Hillebrand MJ, van Leeuwen FE, Lutgerink JT, van Zandwijk N, Jansen HM, Kriek E. Polycyclic aromatic hydrocarbon-DNA adducts in lung tissue from lung cancer patients. Carcinogenesis 11:1677–1681 (1990).

37. Perera FP, Hemminki K, Young TL, Brenner D, Kelly G, Santella RM. Detection of polycyclic aromatic hydrocarbon-DNA adducts in white blood cells of foundry workers. Cancer Res 48:2288–2291 (1988).
38. Poirier MC, Egorin MJ, Fichtinger-Schepman AM, Yuspa SH, Reed E. DNA adducts of cisplatin and carboplatin in tissues of cancer patients. IARC Sci Publ 313–320 (1988).
39. Souliotis VL, Kaila S, Boussiotis VA, Pangalis GA, Kyrtopoulos SA. Accumulation of O^6-methylguanine in human blood leukocyte DNA during exposure to procarbazine and its relationships with dose and repair. Cancer Res 50:2759–2764 (1990).
40. van Delft JH, van den Ende AM, Keizer HJ, Ouwerkerk J, Baan RA. Determination of N^7-methylguanine in DNA of white blood cells from cancer patients treated with dacarbazine. Carcinogenesis 13:1257–1259 (1992).
41. Santella RM, Hemminki K, Tang DL, Paik M, Ottman R, Young TL, Savela K, Vodickova L, Dickey C, Whyatt R, Perera FP. Polycyclic aromatic hydrocarbon-DNA adducts in white blood cells and urinary 1-hydroxypyrene in foundry workers. Cancer Epidemiol Biom Prev 2:59–62 (1993).
42. Santella RM, Yang XY, DeLeo VA, Gasparro FP. Detection and quantification of 8-methoxypsoralen-DNA adducts. In: Methods for Detecting DNA Damaging Agents in Humans Applications in Cancer Epidemiology and Prevention. Vol 89 (Bartsch H, Hemminki K, O'Neill IK, eds). Lyon:International Agency for Research on Cancer, 1988;333–340.
43. Degan P, Shigenaga MK, Park EM, Alperin PE, Ames BN. Immunoaffinity isolation of urinary 8-hydroxy-2′-deoxyguanosine and 8-hydroxyguanine and quantitation of 8-hydroxy-2′-deoxyguanosine in DNA by polyclonal antibodies. Carcinogenesis 12:865–871 (1991).
44. Bruze M, Emmett EA, Creasey J, Strickland PT. Cyclobutadithymidine induction by solar-simulating UV radiation in human skin. II: Individual responses. J Invest Dermatol 93:341–344 (1989).
45. Terheggen PMAB, Begg AC, Emondt JY, Dubbelman R, Floot BGJ, den Engelse L. Formation of interaction products of carboplatin with DNA *in vitro* and in cancer patients. Br J Cancer 63:195–200 (1991).
46. Yang XY, DeLeo V, Santella,RM. Immunological detection and visualization of 8-methoxypsoralen-DNA photoadducts. Cancer Res 47:2451–2455 (1987).
47. Yang XY, Gasparro FP, DeLeo VA, Santella RM. 8-Methoxypsoralen-DNA adducts in patients treated with 8-methoxypsoralen and ultraviolet A light. J Invest Dermatol 92:59–63 (1989).
48. Roza L, De Gruijl FR, Bergen Henegouwen JB, Guikers K, Van Weelden H, Van Der Schans GP, Baan RA. Detection of photorepair of UV-induced thymine dimers in human epidermis by immunofluorescence microscopy. J Invest Dermatol 96:903–907 (1991).
49. Weston A. Physical methods for the detection of carcinogen-DNA adducts in humans. Mutat Res 288:19–29 (1993).
50. Kang HI, Konishi C, Eberle G, Rajewsky MF, KurokiT, Huh NH. Highly sensitive, specific detection of O^6-methylguanine, O^4-methylthymine, and O^4-ethylthymine by the combination of high-performance liquid chromatography prefractionation, ^{32}P-postlabeling, and immunoprecipitation. Cancer Res 52:5307–5312 (1992).
51. Kato S. Petruzzelli S, Bowman ED, Turteltaub KW, Blomeke B, Weston A, Shields PG. 7-Alkyldeoxyguanosine adduct detection by two-step HPLC and the ^{32}P-postlabeling assay. Carcinogenesis 14:545–550 (1993).
52. Cuzick J, Routledge MN, Jenkins D, Garner RC. DNA adducts in different tissues of smokers and nonsmokers. Int J Cancer 45:673–678 (1990).
53. Geneste O, Camus AM, Castegnaro M, Petruzzelli S, Macchiarini P, Angeletti CA, Giuntini C, Bartsch H. Comparison of pulmonary DNA adduct levels, measured by ^{32}P-postlabelling and aryl hydrocarbon hydroxylase activity in lung parenchyma of smokers and ex-smokers. Carcinogenesis 12:1301–1305 (1991).
54. Hemminki K, Perera FP, Phillips DH, Randerath K, Reddy, MV, Santella RM. Aromatic deoxyribonucleic acid adducts in white blood cells of foundry and coke oven workers. Scand J Work Environ Health 14(Suppl 1):55–56 (1988).
55. Hemminki K, Perera FP, Phillips DH, Randerath K, Reddy MV, Santella RM. Aromatic DNA adducts in white blood cells of foundry workers. IARC Sci Publ 89:190–195 (1988).
56. Perera FP, Hemminki K, Gryzbowska E, Motykiewicz G, Michalska J, Santella RM, Young TL, Dickey C, Brandt–Rauf, DeVivo P, Blaner I, Tsai WY, Chorazy M. Molecular and genetic damage in humans from environmental pollution in Poland. Nature 360:256–258 (1992).
57. Shields PG, Povey AC, Wilson VL, Weston A, Harris CC. Combined high-performance liquid chromatography/^{32}P-postlabeling assay of *N*7-methyldeoxyguanosine. Cancer Res 50:6580–6584 (1990).
58. Shields PG, Harris CC, Petruzzelli S, Bowman ED, Weston A. Standardization of the ^{32}P-postlabeling assay for polycyclic aromatic hydrocarbon DNA adducts. Mutagenesis 8:121–126 (1993).
59. Gorelick NJ. Application of HPLC in the ^{32}P-postlabeling assay. Mutat Res 288:5–18 (1993).
60. Moller L, Zeisig M, Vodicka P. Optimization of an HPLC method for analyses of ^{32}P-postlabeled DNA adducts. Carcinogenesis 14:1343–1348 (1993).
61. Weston A, Bowman ED. Fluorescence detection of benzo[*a*]-pyrene-DNA adducts in human lung. Carcinogenesis 12:1445–1449 (1991).
62. Weston A, Bowman ED. Shields PG, Trivers GE, Poirier MC, Santella RM, Manchester DK. Detection of polycyclic aromatic hydrocarbon-DNA adducts in human lung. Environ Health Perspect 99:257–259 (1993).
63. Harris CC, LaVeck G, Groopman J, WilsonVL, Mann D. Measurement of aflatoxin B_1, its metabolites, and DNA adducts by synchronous fluorescence spectrophotometry. Cancer Res 46:3249–3253 (1986).
64. Vahakangas K, Haugen A, Harris CC. An applied synchronous fluorescence spectrophotometric assay to study benzo[*a*]pyrene-diolepoxide-DNA adducts. Carcinogenesis 6:1109–1115 (1985).
65. Harris CC, Vahakangas K, Newman MJ, Trivers GE, Shamsuddin A, Sinopoli N, Mann DL, Wright WE. Detection of benzo[*a*]pyrene diol epoxide-DNA adducts in peripheral blood lymphocytes and antibodies to the adducts in serum from coke oven workers. Proc Natl Acad Sci USA 82:6672–6676 (1985).
66. Weston A, Rowe ML, Manchester DK, Farmer PB, Mann DL, Harris CC. Fluorescence and mass spectral evidence for the formation of benzo[*a*]pyrene anti-diol-epoxide-DNA and -hemoglobin adducts in humans. Carcinogenesis 10:251–257 (1989).
67. Corley J, HurtubisemRJ, Bowman ED, Weston A. Solid matrix, room temperature phosphorescence identification and quantitation of the tetrahydrotetrols derived from the acid hydrolysis of benzo[*a*]pyrene-DNA adducts from human lung. Carcinogenesis 16:423–426 (1995).
68. Corley JS, Hurtubise RJ. Luminescence properties and analytical figures of merit of the tetrols of benzo[*a*]pyrene-DNA adducts adsorbed on α-, β- and τ- cyclodextrin/NaCl mixtures [Abstract]. Anal Lett 25:1559–1572 (1993).
69. Groopman JD, Sabbioni G, Wild CP. Molecular dosimetry of human aflatoxin exposures. In: Molecular Dosimetry and Human Cancer (Groopman JD, ed). Boca Raton, FL:CRC Press. 1991;303–324.
70. Herron DC, Shank RC. Methylated purines in human liver DNA after probable dimethylnitrosamine poisoning. Cancer Res 40:3116–3117 (1993).
71. Watson WP, Smith RJ, Huckle KR, Wright AS. Comparison of hydrocarbon DNA adducts formed in mouse and human skin following treatment with benzo[*a*]pyrene. Arch Toxicol (Suppl 11):93–98 (1987).
72. Farmer PB, Shukern EG, Bird I. DNA and protein adducts as indicators of *in vivo* methylation by nitrosatable drugs. Carcinogenesis 7:9–52 (1986).

73. Farmer PB, Bailey E, Green JA, Leung CS, Manson MM. Biomonitoring of human exposure to alkylating agents by measurement of adducts to haemoglobin or DNA. IARC Sci Publ 109:71–77 (1991).
74. Bryant MS, Skipper PL, Tannenbaum SR, Maclure, M. Hemoglobin adducts of 4-aminobiphenyl in smokers and nonsmokers. Cancer Res 47:602–608 (1987).
75. Bryant MS, Vineis P, Skipper PL, Tannenbaum SR. Hemoglobin adducts of aromatic amines: associations with smoking status and type of tobacco. Proc Natl Acad Sci USA 85:9788–9791 (1988).
76. Hecht SS, Haley NJ, Hoffman D. Monitoring exposure to tobacco products by measurement of nicotine metabolites and derived carcinogens. In: Molecular Dosimetry and Human Cancer (Groopman JD, ed). Boca Raton, FL:CRC Press, 1991;325–361.
77. Shuker DE. Nucleic acid-carcinogen adducts in human dosimetry. Arch Toxicol Suppl 13:55–65 (1989).
78. Farmer PB. Analytical approaches for the determination of protein-carcinogen adducts using mass spectrometry. In: Molecular Dosimetry and Human Cancer (JD Groopman, ed). Boca Raton, FL:CRC Press, 1991;189–210.
79. Stillwell WG, Glogowski J, Xu HX, Wishnok JS, Zavala D, Montes G, Correa P, Tannenbaum SR. Urinary excretion of nitrate, *N*-nitrosoproline, 3-methyladenine, and 7-methylguanine in a Colombian population at high risk for stomach cancer. Cancer Res 51:190–194 (1991).
80. Prevost V, Shuker DE, Friesen MD, Eberle G, Rajewsky MF, Bartsch H. Immunoaffinity purification and gas chromatography-mass spectrometric quantification of 3-alkyladenines in urine: metabolism studies and basal excretion levels in man. Carcinogenesis 14:199–204 (1993).
81. Foiles PG, Akerkar SA, Carmella SG, Kagan M, Stoner GD, Resau JH, Hecht SS. Mass spectrometric analysis of tobacco-specific nitrosamine-DNA adducts in smokers and nonsmokers. Chem Res Toxicol 4:364–368 (1991).
82. Manchester, DK, Weston A, Choi JS, Trivers GE, Fennessey PV, Quintana E, Farmer PB, Mann DL, Harris CC. Detection of benzo[*a*]pyrene diol epoxide-DNA adducts in human placenta. Proc Natl Acad Sci USA 85:9243–9247 (1988).
83. Lin D, Lay JO, Bryant MS, Malaveille C, Friesen M, Bartsch H, Lang NP, Kadlubar FF. Analysis of 4-aminobiphenyl-DNA in human urinary bladder and lung by alkaline hydrolysis and negative ion gas chromatography-mass spectrometry. Environ Health Perspect 102:11–16 (1993).
84. Friesen MD, Kaderlik K, Lin D, Garren L, Bartsch H, Lang NP, Kadlubar FF. Analysis of DNA adducts of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine in rat and human tissues by alkaline hydrolysis and gas chromatography-electron capture mass spectrometry: validation by comparison with ^{32}P-postlabeling. Chem Res Toxicol 7:733–739 (1994).
85. Fichtinger-Schepman AMJ, van der Velde-Visser SD, van Dijk-Knijnenburg HCM, van Oosterom AT, Baan RA, Berends F. Kinetics of the formation and removal of cisplatin-DNA adducts in blood cells and tumor tissue of cancer patients receiving chemotherapy: comparison with *in vitro* adduct formation. Cancer Res 50:7887–7894 (1990).
86. Poirier MC, Reed E, Litterst CL, Katz D, Gupta-Burt S. Persistence of platinum-ammine-DNA adducts in gonads and kidneys of rats and multiple tissues from cancer patients. Cancer Res 52:149–153 (1992).
87. Plooy AC, Fichtinger-Schepman AM, Schutte HH, van Dijk M, Lohman PH. The quantitative detection of various Pt-DNA-adducts in Chinese hamster ovary cells treated with cisplatin: application of immunochemical techniques. Carcinogenesis 6:561–566 (1985).
88. Reed E, Gupta-Burt S, Litterst CL, Poirier MC. Characterization of the DNA damage recognized by an antiserum elicited against *cis*-diamminedichloroplatinum (II)-modified DNA. Carcinogenesis 11:2117–2121 (1990).
89. Dahman EAMF. Introduction. In: Electroanalysis: Theory and Applications in Aqueous and Non-aqueous Media and in Automated Chemical Control. Amsterdam:Elsevier, 1986;3–9.
90. Stulik K, Pacakova V. Selected applications of electrochemical detectors in flowing liquids. In: Electroanalytical Measurements in Flowing Liquids (Chalmers RA, Masson M, Miller JN, eds). Chichester, U.K.:Ellis Horwood, 1987;11–26.
91. Stulik K, Pacakova V. Selected applications of electrochemical detectors in flowing liquids. In: Electroanalytical Measurements in Flowing Liquids (Chalmers RA, Masson M, eds). Chichester, U.K.:Ellis Horwood, 1987;204–279.
92. Kasai H, Crain PF, Kuchino Y, Nishimura S, Ootsuyama A, Tanooka H. Formation of 8-hydroxyguanine moiety in cellular DNA by agents producing oxygen radicals and evidence for its repair. Carcinogenesis 7:1849–1851 (1986).
93. Shigenaga MK, Gimeno CJ, Ames BN. Urinary 8-hydroxy-2′-deoxyguanosine as a biological marker of *in vivo* oxidative DNA damage. Proc Natl Acad Sci USA 86:9697–9701 (1989).
94. Kiyosawa H, Suko M, Okudaira H, Murata K, Miyamoto T, Chung MH, Kasai H, Nishimura S. Cigarette smoking induces formation of 8-hydroxydeoxyguanosine, one of the oxidative DNA damages in human peripheral leukocytes. Free Radic Res Commun 11:23–27 (1990).
95. Wilson VL, Basu AK, Essigmann JM, Smith RA, Harris CC. O^6-Alkyldeoxyguanosine detection by ^{32}P-postlabeling and nucleotide chromatographic analysis. Cancer Res 48:2156–2161 (1988).
96. Santella RM, Weston A, Perera FP, Trivers GT, Harris CC, Young TL, Nguyen D, Lee BM, Poirier MC. Interlaboratory comparison of antisera and immunoassays for benzo[*a*]pyrene-diol-epoxide-I-modified DNA. Carcinogenesis 9:1265–1269 (1988).
97. Weston A, Beland FA, Manchester DK, Parker NB, Harris CC, Poirier MC. Development of preparative immunoaffinity chromatography for the isolation of aromatic amine-DNA adducts from humans. Proc Am Assoc Cancer Res 30:134 (1989).
98. Weston A, Manchester DK, Poirier MC, Choi JS, Trivers GE, Mann DL, Harris CC. Derivative fluorescence spectral analysis of polycyclic aromatic hydrocarbon-DNA adducts in human placenta. Chem Res Toxicol 2:104–108 (1989).
99. Manchester DK, Wilson VL, Hsu IC, Choi JS, Parker NB, Mann DL, Weston A, Harris CC. Synchronous fluorescence spectroscopic, immunoaffinity chromatographic and ^{32}P-postlabeling analysis of human placental DNA known to contain benzo[*a*]pyrene diol epoxide adducts. Carcinogenesis 11:553–559 (1990).
100. Shields PG, Bowman ED, Harrington AM, Doan VT, Weston A. Polycyclic aromatic hydrocarbon-DNA adducts in human lung and cancer susceptibility genes. Cancer Res 53:3486–3492 (1993).
101. Bianchini F, Montesano R, Shuker DEG, Cuzick J, Wild CP. Quantification of 7-methyldeoxyguanosine using immunoaffinity purification and HPLC with electrochemical detection. Carcinogenesis 14:1677–1682 (1993).
102. Groopman JD, Hasler JA, Trudel LJ, Pikul A, Donahue PR, Wogan GN. Molecular dosimetry in rat urine of aflatoxin-N7-guanine and other aflatoxin metabolites by multiple monoclonal antibody affinity chromatography and immunoaffinity-high performance liquid chromatography. Cancer Res 52:267–274 (1992).
103. Groopman JD, Zhu JQ, Donahue PR, Pikul A, Zhang LS, Chen JS, Wogan GN. Molecular dosimetry of urinary aflatoxin-DNA adducts in people living in Guangxi Autonomous Region, People's Republic of China. Cancer Res 52:45–52 (1992).
104. Cooper DP, Griffin KA, Povey AC. Immunoaffinity purification combined with ^{32}P-postlabeling for the detection of O^6-methylguanine in DNA from human tissues. Carcinogenesis 13:469–475 (1992).
105. Hemminki K, Randerath K, Reddy MV, Putman KL, Santella RM, Perera F, Young TL, Phillips DH, Hewer A, Savela K. Postlabeling and immunoassay analysis of polycyclic aromatic hydrocarbons-adducts of deoxyribonucleic acid in white blood

cells of foundry workers. Scand J Work Environ Health 16:158–162 (1990).
106. Poirier MC, Schoket B, Weston A, Rothman N, Scott B, Deeter DP. Blood cell polycyclic aromatic hydrocarbon (PAH)-DNA adducts and PAH urinary metabolites in soldiers exposed to Kuwaiti oil well fires. Proc Am Assoc Cancer Res 35:569:95 (1994).
107. Grzybowska E, Hemminki K, Szeliga J, Chorazy M. Seasonal variation of aromatic DNA adducts in human lymphocytes and granulocytes. Carcinogenesis 14:2523–2526 (1993).
108. Mumford JL, Lee X, Lewtas J, Young TL, Santella RM. DNA adducts as biomarkers for assessing exposure to polycyclic aromatic hydrocarbons in tissues from Xuan Wei women with high exposure to coal combustion emissions and high lung cancer mortality. Environ Health Perspect 99:83–87 (1993).
109. van Schooten FJ, van Leeuwen FE, Hillebrand MJ, de Rijke ME, Hart AA, van Veen HG, Oosterink S, Kriek E. Determination of benzo[*a*]pyrene diol epoxide-DNA adducts in white blood cell DNA from coke-oven workers: the impact of smoking. J Natl Cancer Inst 82: 927–933 (1990).
110. Hemminki K, Grzybowska E, Chorazy M, Twardowska-Saucha K, Sroczynski JW, Putman KL, Randerath K, Phillips DH, Hewer A, Santella RM, Young TLl, Perera FP. DNA adducts in human environmentally exposed to aromatic compounds in an industrial area of Poland. Carcinogenesis 11:1229–1231 (1990).
111. Poirier MC, Santella R, Weinstein IB, Grunberger D, Yuspa S. Quantitation of benzo[*a*]pyrene-deoxyguanosine adducts by radioimmunoassay. Cancer Res 40:412–416 (1980).
112. Schoket B, Doty WA, Vincze I, Strickland PT, Assennato G, Poirier MC. Increased sensitivity for determination of polycyclic aromatic hydrocarbon-DNA adducts in human DNA samples by dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA). Cancer Epidemiol Biomark Prev 2:349–353 (1993).
113. Rothman N, Correa-Villasenor A, Ford DP, Poirier MC, Haas R, Hansen JA, O'Toole T, Strickland PT. Contribution of occupation and diet to white blood cell polycyclic aromatic hydrocarbon-DNA adducts in wildland firefighters. Cancer Epidemiol Biomark Prev 2:341–348 (1993).
114. Groopman JD, Trudel LJ, Donahue PR, Marshak-Rothstein A, Wogan GN. High-affinity monoclonal antibodies for aflatoxins and their application to solid-phase immunoassays. Proc Natl Acad Sci USA 81:7728–7731 (1984).
115. Poirier MC, Reed E, Zwelling LA, Ozols RF, Litterst CL, Yuspa SH. The use of polyclonal antibodies to quantitate *cis*-diamminedichloroplatium (II)-DNA adducts in cancer patients and animal models. Environ Health Perspect 62:89–94 (1985).
116. Reed E, Yuspa SH, Zwelling LA, Ozols RF, Poirier MC. Quantitation of cisplatin-DNA intrastrand adducts in testicular and ovarian cancer patients receiving cisplatin chemotherapy. J Clin Invest 77:545–550 (1986).
117. Kyrtopoulos SA, Souliotis VL, Valavanis C, Boussiotis VA, Pangalis GA. Accumulation of O^6-methylguanine in human DNA after therapeutic exposure to methylating agents and its relationship with biological effects. Environ Health Perspect 99:143–147 (1993).
118. Poirier MC. Human DNA adduct determinations: Applications in clinical treatment. In: Therapeutic Aspects and Analytical Methods in Cancer Research (Constantin E, ed). Strasbourg, France:Amudes Publications, 1994;19–35.
119. Alexandrov K, Rojas M, Geneste O, Castegnaro M, Camus AM, PetruzzelliS, Giuntini C, Bartsch H. An improved fluorometric assay for dosimetry of benzo[*a*]pyrene diol-epoxide-DNA adducts in smokers' lung: comparisons with total bulky adducts and aryl hydrocarbon hydroxylase activity. Cancer Res 52:6248–6253 (1992).
120. Santella RM, Perera, FP, Young TL, Zhang YJ, Chiamprasert S, Tang D, Wang LW, Beachman A, Lin JH, DeLeo VA. Polycyclic aromatic hydrocarbon-DNA and protein adducts in coal tar treated patients and controls and their relationship to glutathione *S*-transferase genotype. Mutat Res 334:117–124 (1995).
121. Jongeneelen FJ. Biological monitoring of environmental exposure to polycyclic aromatic hydrocarbons; 1-hydroxypyrene in urine of people. Toxicol Lett 72:205–211 (1994).
122. VanRooij JG, Bodelier-Bade MM, Hopmans PM, Jongeneelen FJ. Reduction of urinary 1-hydroxypyrene excretion in coke-oven workers exposed to polycyclic aromatic hydrocarbons due to improved hygienic skin protective measures. Ann Occup Hyg 38:247–256 (1994).
123. Weston A, Bowman ED, Carr P, Rothman N, Strickland PT. Detection of metabolites of polycyclic aromatic hydrocarbons in human urine. Carcinogenesis 14:1053–1055 (1993).
124. Strickland PT, Kang D, Bowman ED, Fitzwilliam A, Downing TE, Rothman N, Groopman JD, Weston A. Identification of 1-hydroxypyrene glucuronide as a major pyrene metabolite in human urine by synchronous fluorescence spectroscopy and gas chromatography-mass spectrometry. Carcinogenesis 15:483–487 (1994).
125. Day BW, Naylor S, Gan LS, Sahali Y, Nguyen TT, Skipper PL, Wishnok JS, Tannenbaum SR. Molecular dosimetry of polycyclic aromatic hydrocarbon epoxides and diol epoxides via hemoglobin adducts. Cancer Res 50:4611–4618 (1990).
126. Melikian AA, Sun P, Amin S, Hecht SS. Gas chromatography-mass spectrometry (GC-MS) characterization of polycyclic aromatic hydrocarbon (PAH)-derived globin adducts in smokers. Proc Am Assoc Cancer Res 36:667:112 (1995).
127. Ferreira MF Jr, Tas S, dell'Omo M, Goormans G. Buchet JP Lauwerys R. Determinants of benzo[*a*]pyrenediol epoxide adducts to haemoglobin in workers exposed to polycyclic aromatic hydrocarbons. Occup Environ Med 51:451–455 (1994).
128. Perera FP, Tang DL, O'Neill JP, Bigbee WL, Albertini RJ, Santella R, Ottman R, Tsai WY, Dickey C, Mooney LA. HPRT and glycophorin A mutations in foundry workers: relationship to PAH exposure and to PAH-DNA adducts. Carcinogenesis 14:969–973 (1993).
129. Perera FP, Dickey C, Santella R, O'Neill JP, Albertini RJ, Ottman R, Tsai WY, Mooney LA, Savela K, Hemminki K. Carcinogen-DNA adducts and gene mutation in foundry workers with low-level exposure to polycyclic aromatic hydrocarbons. Carcinogenesis 15:2905–2910 (1994).
130. Wilson VL, Weston A, Manchester DK, Trivers GE, Roberts DW, Kadlubar FF, Wild CP, Montesano R, Willey JC, Mann, DL, Harris CC. Alkyl and aryl carcinogen adducts detected in human peripheral lung. Carcinogenesis 10:2149–2153 (1989).
131. Fichtinger-Schepman AM, van Oosterom AT, Lohman PH, Berends F. *cis*-Diamminedichloroplatinum(II)-induced DNA adducts in peripheral leukocytes from seven cancer patients: quantitative immunochemical detection of the adduct induction and removal after a single dose of *cis*-diamminedichloroplatinum(II). Cancer Res 47:3000–3004 (1987).
132. Rothman N, Poirier MC, Baser ME, Hansen JA, Gentile C, Bowman ED, Strickland PT. Formation of polycyclic aromatic hydrocarbon-DNA adducts in peripheral white blood cells during consumption of charcoal-broiled beef. Carcinogenesis 11:1241–1243 (1990).
133. Schoket B, Horkay I, Kösa A, Paldeak L, Hewer A, Grover PL, Phillips DH. Formation of DNA adducts in the skin of psoriasis patients, in human skin in organ culture, and in mouse skin and lung following topical application of coal-tar and juniper tar. J Invest Dermatol 94:241–246 (1990).
134. Kato S, Yamashita K, Kim T, Tajiri T, Onda M, Sato S. Modification of DNA by mitomycin C in cancer patients detected by ^{32}P-postlabeling analysis. Mutat Res 202:85–91 (1988).
135. Kaderlik KR, Talaska G, DeBord DG, Osorio AM, Kadlubar FF. 4,4′-Methylene-bis(2-chloroaniline)-DNA adduct analysis in human exfoliated urothelial cells by ^{32}P-postlabeling. Cancer Epidemiol Biomark Prev 2:63–69 (1993).
136. Pfohl-Leszkowicz A, Grosse Y, Castegnaro M, Nicolov IG, Chernozemsky IN, Bartsch H, Betbeder AM, Creppy EE, Dirheimer G. Ochratoxin A-related DNA adducts in urinary tract tumours of Bulgarian subjects. In: Postlabeling Methods for Detection of DNA Adduct (Phillips DH, Castegnaro M, Bartsch H, eds). 1993;141–148.

137. Lewtas J, Mumford J, Everson RB, Hulka B, Wilcosky T, Kozumbo W, Thompson C, George M, Dobiäs L, Sram R. Comparison of DNA adducts from exposure to complex mixtures in various human tissues and experimental systems. Environ Health Perspect 99:89–97 (1993).
138. Schoket B, Phillips DH, Poirier MC, Vincze I. DNA adducts in peripheral blood lymphocytes from aluminum production plant workers determined by ^{32}P-postlabeling and by enzyme-linked immunosorbent assay (ELISA). Environ Health Perspect 99:307–309 (1993).
139. Jahnke GD, Thompson CL, Walker MP, Gallagher JE, Lucier GW, DiAugustine RP. Multiple DNA adducts in lymphocytes of smokers and nonsmokers determined by ^{32}P-postlabeling analysis. Carcinogenesis 11:205–211 (1990).
140. Bodell WJ, Pongracz K, Kaur S, Burlingame AL, Liu SF, Rappaport SM. Investigation of styrene oxide-DNA adducts and their detection in workers exposed to styrene. Prog Clin Biol Res 340C:271–282 (1990).
141. Vodicka P, Vodickova L, Trejbalova K, Sram RJ, Hemminki K. Persistence of O^6-guanine DNA adducts in styrene-exposed lamination workers determined by ^{32}P-postlabeling. Carcinogenesis 15:1949–1953 (1994).
142. Horvath E, Pongracz K, Rappaport S, Bodell WJ. ^{32}P-postlabeling detection of DNA adducts in mononuclear cells of workers occupationally exposed to styrene. Carcinogenesis 15:1309–1315 (1994).
143. Savela K, Hemminki K. DNA adducts in lymphocytes and granulocytes of smokers and nonsmokers detected by the ^{32}P-postlabeling assay. Carcinogenesis 12:503–508 (1991).
144. Holz O, Krause T, Scherer G, Schmidt-Preuss U, Rudiger HW. ^{32}P-postlabeling analysis of DNA adducts in monocytes of smokers and passive smokers. Int Arch Occup Environ Health 62:299–303 (1990).
145. Randerath K, Miller RH, Mittal D, Randerath E. Monitoring human exposure to carcinogens by ultrasensitive postlabeling assays: application to unidentified genotoxicants. IARC Sci Publ 89:361–367 (1988).
146. Phillips DH, Hewer A, Grover PL, Jass JR. An aromatic DNA adduct in colonic mucosa from patients with colorectal cancer. IARC Sci Publ 89:368–371 (1988).
147. Phillips DH, Hewer A, Grover PL. Aromatic DNA adducts in human bone marrow and peripheral blood leukocytes. Carcinogenesis 7:2071–2075 (1986).
148. Jones NJ, McGregor AD, Waters R. Detection of DNA adducts in human oral tissue: correlation of adduct levels with tobacco smoking and differential enhancement of adducts using the butanol extraction and nuclease P1 versions of ^{32}P-postlabeling. Cancer Res 53:1522–1528 (1993).
149. Spigelman AD, Scates DK, Venitt S, Phillips RK. DNA adducts, detected by ^{32}P-postlabeling, in the foregut of patients with familial adenomatous polyposis and in unaffected controls. Carcinogenesis 12:1727–1732 (1991).
150. Groopman JD, Hall AJ, Whittle H, Hudson GJ, Wogan GN, Ruggero M, Wild CP. Molecular dosimetry of aflatoxin-N7-guanine in human urine obtained in the Gambia, West Africa. Cancer Epidemiol Biomark Prev 1:221–227 (1992).
151. Weston A, Shields PG, Bowman ED. Isolation of polycyclic aromatic hydrocarbon-DNA adducts from human lung. In: Polycyclic Aromatic Compounds (Garrigues P, Lamotte M, eds). Bordeaux, France:Gordon and Breach Science Publishers, 1991;937.
152. Chaudhary AK, Nokubo M, Reddy GR, Yeola SN, Morrow JD, Blair IA, Marnett LJ. Detection of endogenous malondialdehyde-deoxyguanosine adducts in human liver. Science 265:1580–1582 (1994).
153. Reed E, Parker RJ, Gill I, Bicher A, Dabholkar M, Vionnet JA, Bostick-Bruton F, Tarone R, Muggia FM. Platinum-DNA adduct in leukocyte DNA of a cohort of 49 patients with 24 different types of malignancies. Cancer Res 53:3694–3699 (1993).
154. Anonymous. Tobacco smoking. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Lyon:International Agency for Research on Cancer, 1986;83–126.
155. Ichiba M, Hagmar L, Rannug A, Hogstedt B, Alexandrie A-K, Carstensen U, Hemminki K. Aromatic DNA adducts, micronuclei and genetic polymorphism for CYP1A1 and GST1 in chimney sweeps. Carcinogenesis 15:1347–1352 (1994).
156. Rothman N, Shields P, Poirier MC, Harrington A, Ford DP, Strickland PT. The impact of glutathione *S*-transferase M1 and cytochrome P450 1A1 genotypes on white blood cell polycyclic aromatic hydrocarbon-DNA adduct levels in humans. Mol Carcinogenesis 14:63–70 (1995).