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The Potential Usefulness of Biological Markers in Risk Assessment

by Frederica Perera*

Substantial data have been generated during the last 5 years in experimental systems and human populations which shed light on the potential usefulness of biological markers in human cancer risk assessment. Following a brief review of overall progress to date in the biomonitoring of human populations, this paper turns to the growing body of data regarding carcinogen-DNA and protein adducts as illustrative markers of biologically effective dose of carcinogens. The data base illustrates considerable human interindividual variation in binding and the presence of significant "background" levels of adducts—both of which support the absence of human population thresholds for exposure to carcinogens. The contribution of adduct data to our understanding of the shape of low dose-response curve and the reliability of interspecies extrapolation, as well as the relevance of adducts to cancer risk, are also discussed. Even though adducts can now be useful in hazard identification or qualitative risk assessment, more research is needed before they can serve as quantitative predictors of human cancer risk.

Introduction

Human cancer risk assessment is conventionally based on estimates of administered dose and/or human exposure, i.e., the amount of carcinogen in the external environment. Of far greater relevance to risk is the biologically effective dose or the actual amount of carcinogen that has interacted with critical cellular targets such as DNA, RNA, or protein (*1,2*). This paper will summarize progress to date in quantifying biologically effective dose of carcinogens in humans—in particular, DNA and protein adducts—in order to address the question, "How can these biological markers improve quantitative risk assessment?"

Available markers of biologically effective dose include DNA adducts, protein adducts as a surrogate, cytogenetic effects [e.g., chromosomal aberrations (CA), sister chromatid exchange (SCE), and micronuclei (MN)], DNA damage and repair [e.g., unscheduled DNA synthesis (UDS)], and somatic cell mutation [e.g., hypoxanthine(guanine)phosphoribosyltransferase (HPRT) and glycophorin A] (*2–4*). All are relevant to the multistage process of chemical carcinogenesis, which is believed to involve genetic damage at one or more stages (*5–7*). Each of these methods has been applied in at least two human study populations (*2,8*). (Table 1). Significant increases in levels of each of these biological markers have generally been observed in exposed individuals compared to baseline or control values.

There is general agreement that these biomarkers can serve as relevant dosimeters of carcinogens and that significant increases in biologically effective dose connote potentially elevated risk of cancer on the group level. Thus, the markers constitute early warning systems to identify carcinogenic hazards or qualitative risk and can indicate the need for increased surveillance and possibly protective measures in the interests of cancer prevention.

Table 1. Biological markers in humans.[a]

Markers	Exposure	Exposed population
DNA adducts	BP, PAH, *cis-DDP*, psoralen, tobacco, *N*-nitrosamines, AFB_1	Patients, workers, tobacco users
Protein adducts	4-ABP, EtO	Smokers, workers
SCE	EtO, organic solvents, pesticides, herbicides, chemotherapy agents	Workers
Chromosome aberrations	VC, epichlorohydrin, herbicides, EtO, chemotherapy agents	Workers
Micronuclei	Organic solvents, metals	Workers
Unscheduled DNA synthesis	Propylene oxide, EtO, styrene	Workers
Mutation	Chemotherapy, radiation	Technicians, patients

Abbreviations: BP, benzo[a]pyrene; PAH, polycyclic aromatic hydrocarbons; *cis*-DPP, cisplatinum; AFB_1, aflatoxin B_1; 4-ABP, 4-aminobiphenyl; EtO, ethylene oxide; VC, vinyl chloride.
[a] For review see (*2–4,8*).

*Columbia University School of Public Health, Division of Environmental Sciences, 60 Haven Avenue, B-109, New York, NY 10032.

Human Data

Let us turn now to human data regarding DNA and protein adducts, two promising new markers of biologically effective dose. As dosimeters, protein and DNA adducts are highly sensitive and can provide valuable information regarding several different time periods of exposure: granulocytes and monocytes have lifetimes on the order of hours to weeks; hemoglobin, 3 to 4 months; and T- cell lymphocytes, months to years (*9,10*). They can also sum up exposures via all routes; e.g., inhalation, ingestion, dermal absorption; and in combination with nonchemical-specific makers such as SCEs and CAs, they can help tease apart the contribution of individual components of chemical mixtures to which humans are generally exposed.

Disadvantages are that methods are still semi-experimental; most are not well validated in humans since studies to date have involved small numbers, and the relationship between various target tissues and those available for assay, usually peripheral blood cells or urine, is yet to be definitively established for most carcinogens. In addition, adducts are most relevant to exposures to initiating or mutagenic carcinogens and are not suitable for dosimetry of carcinogens that act primarily or uniquely during the promotion stage. There is a major need for biological markers for promoting agents.

A growing body of data regarding DNA and protein adducts in human populations with quantifiable exposures to diverse carcinogens illustrates two important points relevant to quantitative risk assessment (Tables 2 and 3). First, there is significant interindividual variation in binding levels, even when external exposure is comparable. For example, levels of benzo[a]pyrene-DNA (BP-DNA) in smokers of 1 to 2 ppd ranged from nondetectable (ND) to 0.21 fmole adducts/μg DNA, and 4-aminobiphenyl-hemoglobin (4-ABP-Hb) concentrations ranged from 0.44 to 1.5 pmole/g (*11*). In cisplatinum-treated cancer patients, adduct levels ranged from ND to 0.4 fmole/μg (*15*). Significant levels of cisplatinum-DNA (*cis*-DPP-DNA) adducts occurred in only about 50% of subjects receiving standardized doses of chemotherapy while the other half sustained no measurable biological dose (*15*).

Second, there is a significant background in so-called "unexposed" controls, e.g., in worker controls and nonsmokers. In all of the studies summarized in Table 2, the mean values for controls were significantly greater than zero. In all cases there was overlap in DNA adduct levels between exposed and control groups. This is not unexpected given the multiple sources of environmental carcinogens including passive smoking, the food supply, ambient air, etc.

Regarding the low dose-response curve (i.e., exposure-adduct curve) in humans, data are limited, but for reasons just discussed do not indicate a threshold for adduct formation by polycylic aromatic hydrocarbons (PAH), 4-aminobiphenyl (4-ABP), ethylene oxide (EtO), and tobacco smoke constituents. A reasonably linear relationhip was seen between estimated EtO exposure and EtO protein in a small number of sterilization plant workers (*17*). Similarly, the cumulative dose of cisplatinum was linearily related to levels of cisplatinum-DNA adducts in the individuals who formed measurable adducts (*15*).

A recent study of DNA adducts in Finnish iron foundry workers (n = 35) indicates a dose-response for benzo[a]pyrene-DNA (BP-DNA) by immunoassay and a significant increase in adduct levels in exposed individuals compared to controls (*12*). Foundry workers have an increased risk of lung cancer, with highest risk seen for casters (*19*). Based upon this and the other human studies discussed, we can reasonably assume that these workers with significantly elevated adduct levels are at higher risk of cancer than groups who have not received the same high biologically effective dose. Thus, qualitative judgments about risk are possible for the group, but not at the individual level.

Implications for Risk Assessment

But now we ask, "How can DNA and protein adducts improve quantitative risk assessment?" [For a more detailed discussion, see (*8*)]. Here we are constrained to consider animal data pertaining to three fundamental questions: How should we extrapolate from high to low dose, i.e., what is the shape of the low dose-response curve? How reliably can we extrapolate from laboratory

Table 2. Examples of studies of adducts in human populations: DNA adducts in peripheral blood cells.

Marker	Exposure	Population	Range, fmole/μg	Reference
BP-DNA	PAH	Smokers	ND–0.21	(*11*)
		Nonsmokers	ND–0.12	
		Foundry workers	ND–2.24	(*12*)
		Controls	ND–0.24	
O^6-MedGuo	*N*-Nitrosamines	Cancer patients	ND–0.16	(*13*)
		Controls	ND–0.04	
Smoking-related (^{32}P)	Cigarette smoke	Smokers	0.006–0.04	(*14*)
		Nonsmokers	0.012–0.03	
cis-DDP-DNA	Cisplatinum	Patients	ND–0.4	(*15*)

Table 3. Examples of studies of adducts in human populations: Protein adducts in hemoglobin.

Marker	Exposure	Population	Range, pmole/μg	Reference
4-ABP-Hb	Cigarette smoke	Smokers	0.44–1.5	(*11,16*)
		Nonsmokers	0.04–0.3	
EtO-Hb	EtO	Sterilization workers	400–13,500	(*17*)
		Controls	< 50	
EtO-Hb	EtO	Smokers	217–690	(*18*)
		Nonsmokers	27–106	

Table 4. Compounds for which proportionality has been observed between administered dose: Macromolecular binding.

Chemical	Reference
Single-dose studies	
trans-4-Dimethylaminostilbene	(*21*)
N-Nitrosodimethylamine	(*21*)
Methylating/ethylating agents	(*22,23*)
EMS	(*24*)
AFB_1	(*21*)
4-ABP	(*22,23*)
DMN	(*25*)
BP	(*22,23*)
PAH	(*26*)
Sterigmatocystin	(*27*)
Chronic or multiple-dose studies	
trans-4-Acetylaminostilbene	(*21*)
Methylating/ethylating agents	(*22*)
DEN	(*22*)
2-AAF	(*22*)
NNK	(*28*)
MMS	(*22,23*)
4-ABP	(*22,23*)
AFB_1	(*22*)
EtO	(*23*)
Chloroform	(*23*)

Abbreviations: MMS, methylmethanesulfonate; EMS, ethylmethanesulfonate; 2-AAF, 2-acetylaminofluorene; AFB_1, aflatoxin B_1; DEN, dietylnitrosamine; NNK, 4(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone; DMN, dimethylnitrosamine; EtO, ethylene oxide.

animals to humans in calculating risk? What do DNA and protein adducts tell us about risk of cancer?

Regarding the first question, the convention as reaffirmed in the EPA Guidelines on Assessment of Cancer Risk (*20*) is to use a multistage model that assumes additivity on background and hence is linear at low dose. This model is widely considered to be the most biologically plausible of available models, but there are many uncertainties as to the true dose-response relationship, even in the experimental animal.

There have been a number of attempts to test whether low-dose linearity is a valid assumption by comparing administered dose to macromolecular binding in laboratory animals (Table 4). The first set of studies in Table 4 gave a single dose (or in one case a repeat dose), often over a wide range (in one instance 4–5 orders of magnitude). Generally, exposures were considerably higher than those encountered by humans, with the exception of benzo[a]pyrene (*29*). The compounds listed gave a constant ratio between administered dose and binding to DNA and/or protein. In the case of formaldehyde, however, a nonlinear dose-response for putative formaldehyde-DNA-protein cross-links was seen in rats exposed by inhalation during two 6-hr periods (*30*).

Chronic or multiple dose studies have, with few exceptions, shown a constant ratio between administered dose and DNA or protein adducts (Table 4). In addition to low-dose linearity, a plateau in DNA adduct formation was generally observed at higher doses of the carcinogens in Table 4. Only dimethylnitrosamine (DMN) gave a nonlinear dose response regarding protein adduct formation (*23*). Thus, single dose and chronic studies indicate that macromolecular binding is generally proportional to administered dose, in some cases [such as BP and 4-(*N*-methyl-*N*-nitrosamino)-1(3-pyridyl)-1-butanone or NNK)], even at levels similar to environmental concentrations.

With respect to interspecies extrapolation of risk, the currently accepted assumption is that humans are as sensitive as the most sensitive experimental animal species (*20,31*). Comparative DNA and protein binding data across species would shed light on the initial question, "Do humans and test animals receive the same biologically effective dose of carcinogen per unit of exposure?" Obvious factors that are likely to affect binding in humans but not experimental animals include human variability in carcinogen activation, binding, and adduct repair due to environmental and genetic factors; multiplicity of exposures both to the chemical of interest and to other chemicals or agents that are metabolically activated or cleared via the same pathways or that bind to DNA and call upon the same DNA repair systems; and human exposure to agents that can interact (either antagonistically or synergistically) with the chemical exposure of concern to alter binding levels. Thus, even if binding thresholds or nonlinearities were observed in animal experiments, they will not necessarily hold for the diverse human population.

Unfortunately, there is a lack of parallel human and animal chronic exposure data involving similar levels of carcinogen and using comparable methods to evaluate adducts. A serious criticism of the recent attempt to use observed nonlinearity in putative formaldehyde DNA-protein cross-links as a basis for risk estimation (*32*) was that the animal experiment involving two 6-hr exposures to formaldehyde is not necessarily relevant either to the positive cancer bioassay or the human exposure situation.

What do binding levels tell us about quantitative risk of cancer? Here we must turn to experimental data, since there have been no prospective human studies aimed at answering this question.

We might examine this question in two parts: first, what is the relationship between adducts and induction of gene mutation; and second, what about the relationship between adducts and carcinogenicity? Data are limited, but in the few studies where the critical adduct has been identified and measured, there is a good correlation between binding levels and the frequency of induced mutations (*33*). Moreover, the ratio of adducts

to mutations in mammalian cells appears to be about 10:1 for alkylating agents (*34*) and higher (140–190:1) for agents (nitrated pyrenes, benzo[a]pyrene) that form bulky adducts (*35,36*). These calculations are based on the assumptions that about 1000 base pairs are involved in mutation and that DNA modification is uniform across the genome. They should therefore be interpreted cautiously.

With respect to the quantitative relationship between DNA adducts and carcinogenicity, there are three lines of evidence: the positive correlation for PAHs and alkylating agents between the ability to form covalent DNA adducts in experimental animals *in vivo* and their carcinogenic potency (*37,38*); *in vitro* studies quantitatively linking the extent of adduct formation to cell transformation and/or tumor induction (*39*); and elevated adducts in the target organ of sensitive species (*23*). This relationship has not been consistently observed. However, many of these studies have serious limitations: only short-term DNA adduct persistence was monitored, and often total adducts, rather than critical ones, were measured.

A number of factors apparently determine the carcinogenic consequence of DNA adducts, and these must be reasonably well understood and accounted for before any attempt can be made to derive quantitative risk estimates based on binding data. These include the rate of accurate repair prior to replication, levels of critical adduct occurring at the target site and (ideally) the concentration of adducts at vulnerable sites or hot spots on the genome. Determining factors also include the subsequent exposure to agents that cause promotion or progression. Thus, for quantitative risk assessment, at a minimum, we need to identify the critical persistent adduct at the target site or an established surrogate.

One well-developed effort to utilize laboratory and human biomonitoring adduct data to predict risk is that of Ehrenberg et al. for EtO (*40*). Here macromolecular (hemoglobin) binding was experimentally determined to be directly proportional to target tissue dose. Relationships between tissue dose, target, and molecular dose were experimentally determined, as was the tissue dose of EtO that would produce the same number of mutations as a unit of radiation (or the radiation equivalent dose of EtO). EtO-histidine adducts were measured in sterilization plant workers, and the risk of a 1 ppm·hr of EtO exposure was estimated to be equivalent to 10 mrad of radiation (*17*). The workers' average tissue dose of EtO was converted to radiation risk equivalents. Excess cancer risk (leukemia) was predicted, which is similar to that seen in follow-up epidemiological studies of that cohort (*41*). EtO may be a special case in that it is a direct-acting and stable electrophile that distributes uniformly in different tissues.

In summary, this is a challenging and exciting time for both DNA adduct research and risk assessment. To fulfill the promise of a partnership between the two disciplines, we clearly need more parallel chronic exposure data on binding in experimental models and humans as well as prospective studies in animals and model human populations exposed to the same environmental carcinogens.

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