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REVIEW

Basic properties and molecular mechanisms of exogenous chemical carcinogens

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Exogenous chemical carcinogenesis is an extremely complex multifactorial process during which gene–environment interactions involving chronic exposure to exogenous chemical carcinogens (ECCs) and polymorphisms of cancer susceptibility genes add further complexity. We describe the properties and molecular mechanisms of ECCs that contribute to induce and generate cancer. A basic and specific property of many lipophilic organic ECCs including polycyclic aromatic hydrocarbons and polyhalogenated aromatic hydrocarbons is their ability to bioaccumulate in the adipose tissue from where they may be released in the blood circulation and target peripheral tissues for carcinogenesis. Many organic ECCs are procarcinogens and consequently need to be activated by the cytochrome P450 (CYP) system and/or other enzymes before they can adduct DNA and proteins. Because they contribute not only to the cocarcinogenic and promoting effects of many aromatic pollutants but also to their mutagenic effects, the aryl hydrocarbon receptor-activating and the inducible CYP systems are central to exogenous chemical carcinogenesis. Another basic property of ECCs is their ability to induce stable and bulky DNA adducts that cannot be simply repaired by the different repair systems. In addition, following ECC exposure, mutagenesis may also be caused indirectly by free-radical production and by epigenetic alterations. As a result of complex molecular interplays, direct and/or indirect mutagenesis may especially account for the carcinogenic effects of many exogenous metals and metalloids. Because of these molecular properties and action mechanisms, we conclude that ECCs could be major contributors to human cancer, with obviously great public health consequences.

Introduction

There is no doubt that ionizing radiation and micro-organisms such as oncogenic viruses are environmental cancer-causing agents. However, for chemicals, there is persisting debate on the relative contribution to carcinogenesis of endogenous and exogenous molecules that damage DNA and consequently different hypotheses regarding the origin of chemically induced cancers. For some scientists, chemical carcinogenesis appears to be mainly an endogenous process because mutations are thought to arise spontaneously and/or originate from endogenous DNA damage that result from natural metabolic intermediates (1). For others, on the basis of epidemiological and toxicological data, xenochemical exposure may play a major role in carcinogenesis (2–4).

In a review and perspective paper, chemical carcinogenesis has been mainly described on the basis of the endogenous hypothesis (5). This prompted us to systematically review experimental data suggesting that another concept is possible, i.e. that exogenous chemical carcinogens (ECCs) which result from tobacco smoking or from involuntary exposure to environmental chemicals may also be important contributors to carcinogenesis, as it is for micro-organisms and ionizing radiation.

We define exogenous carcinogens as all types of physical, chemical and biological agents that can cause cancer after having penetrated into the organism by respiratory, digestive, cutaneous or other possible contamination routes. We define endogenous carcinogens as all potentially carcinogenic molecules or metabolic intermediates that arise in the organism as a consequence of respiration and/or food intake in people living in a safe non-polluted environment. We exclude active tobacco smoking from the definition of environmental exposure but we include in the definition of environmental chemical carcinogens not only carcinogens resulting from occupational activities and more generally from industrial pollution but also carcinogens that are associated with passive tobacco smoking or overcooking meat. We thus consider overall that ECCs encompass chemicals resulting from active tobacco smoking or from involuntary environmental exposure.

In the present paper, we describe the different properties and molecular mechanisms of exogenous chemicals that contribute to induce and generate cancer, and we discuss the hypothesis according to which these properties and mechanisms may make exogenous chemicals more prone to cause cancer than endogenous natural molecules.

Models of carcinogenesis

Carcinogenesis can be modeled in two stages, 'initiation' and 'promotion' (6,7). In 1954, Foulds (8) individualized a third stage that he termed 'progression', in order to account for all post-initiation events that occur during carcinogenesis. Consequently, it was assumed that human exposure to exogenous chemicals may lead to toxic and carcinogenic hazards (9) and that chemical carcinogenesis comprises the three sequential and successive steps: initiation, promotion and progression (10–12). Despite the fact that this three-stage model appeared a simplified view (12,13), further biological data confirmed that it could be a basic conceptual framework necessary for pertinent experimental designs and fruitful interpretations of carcinogenesis. Indeed, as summarized in Table I, the field of chemical carcinogenesis has changed considerably in the two last decades due to numerous advances made in biochemistry and molecular biology, causing the three-stage model to be characterized more precisely.

Distinction between tumor initiators, promoters and progressors. According to the above-described three-stage model, chemical carcinogens have been distinguished as initiators, promoters and progressors (10,14). We define tumor initiators as carcinogens capable to induce a first driver mutation in a dividing cell, through direct or indirect mutagenesis, so that an initial clone of mutated cells can emerge. We define tumor promoters as non-genotoxic carcinogens capable to cause clonal expansion of initiated cells, i.e. able to induce proliferation of mutated cells and to prevent these cells from apoptotic loss, so the possibility of additional genetic and/or epigenetic changes is preserved (14). We define tumor progressors as

Abbreviations: AA, aromatic amine; ABC, ATP-binding cassette; AhR, aryl hydrocarbon receptor; AP-1, activating protein-1; Arnt, AhR nuclear translocator; B[*a*]P, benzo[*a*]pyrene; CYP, cytochrome P450; DSB, double-strand break; ECC, exogenous chemical carcinogen; EPHX1, epoxide hydrolase 1; GJIC, gap junctional intercellular communication; GSH, glutathione; GST, GSH-S-transferase; HAA, heterocyclic AA; HPAH, high molecular weight PAH; LPAH, low molecular weight PAH; MPO, myeloperoxidase; NAT, *N*-acetyl transferases; NF-κB, nuclear factor kappa B; NOC, *N*-nitroso compound; NQO1, NAD(P)H:quinone oxidoreductase-1; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorobiphenyl; PHAH, polyhalogenated aromatic hydrocarbon; RNS, reactive nitrogen species; ROI, reactive oxygenated intermediate; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; TPA, 12-*O*-tetradecanoyl phorbol-13-acetate; XME, xenobiotic-metabolizing enzyme.

Table I. Recent advances in biochemistry and molecular biology in characterizing chemical carcinogenesis

Method improvement
Experimental induction of cancers
DNA adduct quantification in humans
Genome sequencing
Epigenomics
Polymorphism genetics
Mutagenesis
Cataloguing oncogens and tumor suppressor genes
Clonal (driver) versus non-clonal mutations
Exogenous versus endogenous mutagenesis
Mechanisms of DNA adduction
Site-specific versus non-site-specific adduction
Biological effects of free radicals
Biochemistry and molecular biology
Metabolism of xenobiotics
Low-dose versus high-dose carcinogenesis
Cataloguing environmental carcinogens
Bioaccumulation of exogenous carcinogens in the adipose tissue

carcinogens that advance mutated cells from promotion to progression, i.e. that allow premalignant mutated cells to irreversibly acquire the phenotype of fully malignant cells (15).

Because of their mutagenic properties, tumor initiators and tumor progressors can thus be theoretically clearly distinguished from tumor promoters, whereas among carcinogens, tumor promoters, because they act through epigenetic mechanisms, may be difficult to distinguish from cocarcinogens. Moreover, due to epigenetic pleiotropic cellular effects and multiple mechanisms of disturbance of tissue homeostasis (16), tumor promoters may also be secondarily mutagenic and thus difficult to distinguish from mutagens.

Examples of ECCs. Typical examples of mutagenic ECCs are benzo[*a*]pyrene (B[*a*]P) and other high molecular weight polycyclic aromatic hydrocarbons (HPAHs) that consist of five to seven rings, nitrosamines and other *N*-nitroso compounds (NOCs), aromatic amines (AAs) and heterocyclic AAs (HAAs) and some metals and metalloids. Although they have not been definitively characterized in experimental systems, some carcinogens such as B[*a*]P, benzoyl peroxide, alkylating agents and arsenicals, in addition to their initiating and/or promoting effects, might act more specifically as tumor progressors (10,17), but this needs to be clarified.

Likewise, a typical example of exogenous chemical promoter is the potent phorbol ester, phorbol 12-myristate 13-acetate, also called 12-*O*-tetradecanoyl phorbol-13-acetate (TPA), which has been characterized experimentally by a myriad of associated phenotypic biological properties (18), including mimicry of the transformed phenotype, modulation of cell differentiation and membrane effects (4,19). An explanation of biological pleiotropic effects of TPA comes from its mechanism of action: in contrast to initiators and progressors, TPA does not bind to DNA but instead binds to protein kinase C-α (20,21), which once activated immediately stimulates transcription of several genes, in particular the early genes c-fos and c-jun, and consequently activates activating protein-1 (AP-1) and nuclear factor kappa B (NF-κB) (18). Despite the fact that AP-1 and NF-κB are transcription factors that mediate cell proliferation and apoptosis through the activation of numerous genes, TPA-induced molecular changes are not fully understood yet since TPA can stimulate the proliferation of initiated cells while having minimal effect on nearby normal cells (18). Also another more recently described action mechanism of TPA and of many other carcinogens such as pentachlorophenol (22) and low molecular weight PAHs (LPAHs), which consist of two to four rings with bay regions or bay-like regions (14,23,24), is to selectively block gap junctional intercellular communication (GJIC) (24,25). This suggests a new non-genotoxic mechanism of chemically induced carcinogenesis, since the role of GJIC in normal tissues is to mediate the passage of growth-regulating molecules between neighboring cells (26). Hence, blockage of GJIC between normal and preneoplastic cells could create an appropriate intra-tissue microenvironment, leading preneoplastic cells to escape growth control from normal surrounding cells and therefore contribute to clonal expansion.

In animal experiments, skin carcinogenesis was observed to be associated with preneoplastic local inflammation and consequently chronic inflammation was considered as a possible tumor promotion mechanism. Moreover, in addition to a large number of epidemiologic studies supporting a role for chronic inflammation in carcinogenesis (1), toxicological and biological data led scientists to hypothesize that growth factors and low-dose free radicals produced by inflammatory cells could stimulate the proliferation of initiated cells. Indeed, in response to growth factor stimulation and/or intracellular redox changes, activation of AP-1 and NF-κB has been proved to occur, leading cells to proliferate, as it is the case in experimental TPA-induced promotion (18). More recently, it has become recognized that NF-κB signaling plays a critical role in tumor promotion and progression by controlling the ability of preneoplastic and cancer cells to resist apoptosis-based tumor surveillance mechanisms and by providing a biological link among inflammation, oxidative stress and cancer (27). However, albeit inflammation and oxidative stress are endogenous processes that may account for cancer occurrence through tumor promotion and because they basically are caused by physical, chemical and/or microbial agents such as viruses, bacteria or parasites, the whole process these exogenous agents can induce actually does not refer to endogenous carcinogenesis but indeed to exogenous carcinogenesis.

Endocrine disruptors and immunosuppressors may also be exogenous chemical promoters through pleiotropic biological effects. Typical examples of exogenous chemical promoters with disrupting endocrine properties are bisphenol A (28,29) and polyhalogenated aromatic hydrocarbons (PHAHs) such as dioxins and polychlorobiphenyls (PCBs), while typical examples of exogenous chemical promoters with immunosuppressive effects are PHAHs yet (30) and also pesticides (31), such as phenoxyacetic acids and chlorophenols (32). A basic molecular mechanism accounting for the tumor promotion induced by PHAHs relates to their binding to and activation of the aryl hydrocarbon receptor (AhR), a ligand transcription factor that mediates most, if not all of, toxic responses induced by coplanar aromatic pollutants (33). Indeed, we now know that the AhR and possibly other xenobiotic-metabolizing enzyme (XME) receptors that control XME expression levels can activate not only numerous target genes that encode for XMEs such as the three cytochrome P450 (CYP)1 enzymes of the CYP system but also many genes that control cell cycle progression and apoptosis (34).

In addition, many endogenous natural hormones such as steroid hormones have been shown to be tumor promoters by directly interacting with specific cytoplasmic receptors in hormone-dependent cells, so it clearly appears that tumor promotion may result from endogenous and exogenous promoters.

Complexity of chemical carcinogenesis. Distinction between complete and stage-related chemical carcinogens. Because cell divisions are a prerequisite for mutation occurrence, endogenous and/or exogenous tumor promoters are necessary as for a long time the clone of premalignant mutated cells have not become fully promoter independent. During initiation and promotion, mutagens and promoters must therefore intimately cooperate in order to drive premalignant cells derived from the initiated clone to become fully malignant.

However, carcinogenesis is certainly a more complex multistep multifactorial process than the previously described initiation–promotion–progression paradigm. Whereas some ‘complete’ chemical carcinogens have the capacity to induce and generate all three steps of carcinogenesis, many others because they act specifically at a different carcinogenesis stage need to act together to generate cancer (10,14). Moreover, types, doses of carcinogens and timing of their administration have been shown in laboratory animals to be important determinants in chemically induced carcinogenesis (10).

Contrary to the classical afore-reported three-stage format, it has been shown experimentally that repeated administration of an exogenous promoter alone may increase the risk of cancer occurrence, and this phenomenon has been ascribed hypothetically to an enhanced number of spontaneous mutations as a consequence of increased proliferation of normal cells (35,36). Yet, in some experimental conditions using chemical tumor initiators or progressors at cytotoxic dose or complete carcinogens at sufficient dose, aneuploidy with subsequent development of cancer may occur apparently in the absence of promotion—more precisely in the absence of exogenous promoter (37). Ignoring the clastogenic effect of complete exogenous carcinogens and the pleiotropic effects of many tumor promoters may thus result in false-negative conclusions concerning the ubiquitous presence and presumably underestimated role of xenochemicals in carcinogenesis.

Distinction between carcinogens and cocarcinogens. By definition, carcinogens are cancer-causing agents, whereas cocarcinogens are not carcinogenic agents, rather agents that can activate carcinogens and/or enhance their carcinogenic effects. Accordingly, xenochemicals such as PAHs, NOCs, AAs, HAAs and PHAHs such as dioxins, PCBs and organochlorine pesticides are exogenous carcinogens, whereas chemicals that deplete the organism of endogenous detoxifying proteins such as glutathione (GSH) (38), that inhibit phase I and/or phase II XMEs (39), that loosely couple the detoxifying effects of phase I oxidative enzymes and of phase II-conjugating enzymes (40), that inhibit DNA repair enzymes (41) or conversely that activate procarcinogens into carcinogens through induction of the CYP system are all cocarcinogens.

Multitude and diversity of ECCs

Tobacco smoking-related carcinogens. Tobacco smoking is a lifestyle-related factor that has clearly been proved to be associated with an increased risk of several types of cancers by epidemiological studies (42,43).

Indeed, on the basis of comprehensive toxicological data, tobacco smoking-related cancers clearly appear to be caused by ECCs resulting from tobacco combustion, since tobacco smoke and tars contain >40 known tumor mutagens and/or promoters (44), such as PAHs, NOCs, AAs and HAAs, acrolein, ethylene oxide and 1,3-butadiene—so a mixture of ECCs equivalent to a complete carcinogen. This finding explains why tobacco smoking is in itself causally implicated in cancer occurrence.

An important observation based on studies of the different PAHs detected in cigarette smoke is that LPAHs that are associated with tumor-promoting effects are in fact in a much higher quantity than HPAHs such as B[*a*]P, which are associated with both promoting and mutagenic properties (45). This strongly suggests that in cigarette smoke, mutagens other than HPAHs, such as NOCs, AAs, HAAs and acrolein could also contribute to induce and generate the complete carcinogenic process in association with LPAHs (46). However, there seems to be some organ target specificity of mutagenic carcinogens since the excess of bladder cancer in smokers is attributable to AAs and HAAs while it seems to be mainly attributable to PAHs for tobacco smoking-related lung cancer (47).

Environmental carcinogens. These considerations might apply to the numerous xenochemicals present at low dose in the environment, where they may constitute mixtures of carcinogens and cocarcinogens and therefore result in complete carcinogenesis through 'cocktail' effects (48,49). However, contrary to active tobacco smoking and occupational exposure, which can be easily individualized as risk factors, risk factors for the general population involuntarily exposed to environmental chemicals cannot be clearly individualized. This makes cancer risk assessment in the general population extremely difficult and thus adds to the uncertainty of establishing causal links between environmental pollutants and human cancer. This explains the persisting gap between the numerous environmental chemical pollutants that have been identified as potentially carcinogenic in humans by the International Agency for Research on Cancer on the basis of experimental data and the scarcity of current results of epidemiological studies showing an associative link between these pollutants and cancer.

Even so, an indirect argument that supports the hypothesis of an underestimated role of air pollution in carcinogenesis is passive tobacco smoking, which has been clearly shown to be a risk factor associated with lung cancer occurrence (50). Also, environmental chemicals may be found at low dose in food (51), as it is the case for PAHs (52), AAs (47), NOCs (53) and for aflatoxins in some areas worldwide (54), suggesting that cancer occurrence may also result from repeated ingestion of low-dose food contaminants. Likewise, an indirect argument that supports this hypothesis is the detection of HAAs produced at high temperatures in overcooking meat or other foodstuff (55) and the finding that among HAAs 2-amino-3-methyl imidazo[4,5-f]quinoline is mutagenic a thousand times more than B[*a*]P at the Ames test (56), whereas 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, albeit far less mutagenic than 2-amino-3-methyl imidazo[4,5-f]quinoline (56), has been proved to cause cancer in animals (57).

On the basis of a systematic review of epidemiological and toxicological data, we therefore have established a list of occupational and environmental chemicals rated as certainly, probably or possibly carcinogenic in humans by International Agency for Research on Cancer that may contaminate air, water and food (3,58). These chemicals include industrial intermediates, air pollutants, agriculture chemicals and food additives, which are potentially carcinogenic or cocarcinogenic in animals and humans. Table II summarizes our attempt to classify some of these occupational and/or environmental chemicals according to their mutagenic, promoting and/or cocarcinogenic effects. In addition, Table III lists some pharmaceuticals and cosmetics with possible (59) or proved carcinogenic effects. Of particular public health concern are anticancer hormonal drugs such as anti-estrogens (60), cytotoxic anticancer drugs such as alkylating agents (61), hormonal drugs such as oral contraceptives (62) and post-menopausal hormone replacement therapy (63) and among cosmetics hair dyes (64,65) and possibly estrogen-like molecules such as parabens (66).

Biochemical properties of organic ECCs

Many organic ECCs are characterized by biochemical properties that clearly distinguish them from endogenous carcinogens.

Lipophilicity as a key property. ECCs may directly damage DNA or indirectly do so after activation into DNA-reactive intermediates or free-radical production. A basic property that distinguishes ECCs from potentially carcinogenic endogenous molecules is that they need to enter cells for carcinogenic activation and DNA damage induction, whereas endogenous molecules, since many of them are naturally occurring intracellular metabolic intermediates, need not. All organisms use a cell membrane as a hydrophobic permeability barrier that specifically selects substrates from the extracellular milieu to control access to their internal milieu. Unlike polar (hydrophilic) organic molecules and many metals and metalloids that are frequently transported actively to the intracellular milieu through endogenous receptors, membrane-bound transporters or ion channels (34,67), non-polar (hydrophobic) organic molecules including many ECCs—but not all—can generally enter cells passively because of their lipophilicity. This is the case for PHAHs such as dioxins, PCBs and organochlorine pesticides and for other organic pollutants such as PAHs and benzene that need first entering cells for metabolization into polar by-products by phase I detoxification enzymes (34,68). Despite the fact that human bodies have evolved inducible enzymatic detoxification and DNA repair systems for millions of years for efficient protection against natural toxic non-polar exogenous chemicals, given the tremendous amount and diversity of chemical pollutants that have recently permeated the environment, these systems may be saturated by excess toxicants while being not fully adapted for complete

detoxification of all man-made molecules. Because the organism could not fully metabolize and inactivate all non-polar exogenous chemicals, this would explain why lipophilic carcinogenic environmental pollutants such as PAHs and PHAHs can bioaccumulate in the adipose tissue and be toxic (69).

Adipose tissue as a reservoir of organic ECCs. Several epidemiologic studies have concluded that overweight/obesity is a risk factor for cancer that contributes to the increased mortality and morbidity associated with several cancer types (70).

We have proposed that in addition to its endocrine function, adipose tissue can act as a reservoir for lipophilic ECCs. Lipophilic exogenous chemicals can be stored in adipocytes, from which they may be permanently released in the blood circulation during lipolysis (71) and/or following apoptosis, and consequently could target peripheral tissues *in vivo* for tumor initiation and promotion (69).

We have experimentally shown that adipocytes are capable of storing liposoluble ECCs such as dioxins (71) and PAHs (72). And we have evidenced that these liposoluble exogenous molecules can be released from adipocytes during lipolysis (71). Moreover, we have shown that among PAHs, B[*a*]P is a key molecule in exogenous chemical carcinogenesis, since it does not only contribute to generate cancer through direct mutagenesis but also increase the adipose tissue mass, so enhancing its function of reservoir for ECCs (72,73). Indeed, it has been shown that in addition to dioxins and PAHs, organochlorines such as organochlorine pesticides (74), PCBs, dioxin-like PCBs, polychlorodibenzo-*p*-dioxins and polychlorodibenzofurans (75) and other chemical pollutants such as polybrominated flame retardants and phthalate esters (76,77) can bioaccumulate in the adipose tissue.

Finally, since lipophilic exogenous chemicals rated as carcinogenic or potentially carcinogenic to humans can bioaccumulate in the adipose tissue and be steadily released in the blood circulation, these findings further support the hypothesis that low-dose environmental carcinogens may contribute to carcinogenesis. However, because many ECCs are procarcinogens, they first need to be activated into DNA-reactive molecules for displaying their carcinogenic effects.

Metabolic activation of organic exogenous procarcinogens

It has been estimated that whereas ~25% of all carcinogens such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin are directly carcinogenic, 75% such as B[*a*]P, benzene or 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine require metabolic activation to reactive oxygenated intermediates (ROIs) to be mutagenic and carcinogenic (34)

Indeed, a number of complex and interactive intracellular metabolic pathways have been shown to activate or inactivate xenochemicals (78,79). An important condition determining fast or slow metabolization of carcinogens is their chemical structure. For example, PAHs or PHAHs that contain two adjacent non-substituted C atoms in aromatic ring are usually metabolized and excreted fastly, whereas PAHs or PHAHs that lack the presence of two adjacent unoccupied C atoms are metabolized slowly, with half-life ranging from weeks to years. Moreover, because of their strong affinity for the AhR, slowly degraded coplanar PAHs and PHAHs are potent inducers of CYP1 enzymes that can activate procarcinogens and contribute independently to carcinogenesis by altering cell cycle functions (34). Many enzymes involved in the metabolic detoxification or activation of procarcinogens are inducible; hence, their activity may be modified by additional environmental exposures, hormones and diet, a finding which adds further difficulty in assessing environment-related cancer risk (80).

Normally, the host is able to detoxify many exogenous chemical pollutants, thanks to phase I and phase II XMEs that in addition to phase II-conjugating proteins such as GSH and to efflux pump proteins such as transporters of the family of ATP-binding cassette (ABC) are involved in the metabolism of xenobiotics (Table IV).

Table II. Categorization of some environmental chemicals according to their carcinogenic and/or cocarcinogenic properties (58)

	Mutagen	Promoter	Cocarcinogen
Acrolein[a]	M		
2-Acetylaminofluorene[b]	M	P	C
Air fine particles[c]			C
Arylamines[d]	M		
Asbestos	M		C
Azoic dyes	M		
Bisphenol A	M	P	
β Naphylamine	M		
Benzene and related molecules	M		C
1,3-Butadiene	M		C
Phthalates[e]	M	P	
Dioxins	M	P	C
Formaldehyde and other related molecules	M		
Hormonal residues[f]		P	
Metals, metalloids	M		C
NOCs[g]	M		
Nitric oxide		P	C
PHAHs[h]	M (some)	P	
PAHs[i]	M	P	C
PCBs	M (some)	P	C (some)
Pesticides[j]	M (some)	P	
Vinyl chlorides (monomers)	M		

[a]Acrolein is contained in cigarette smoke and traffic exhaust.
[b]2-Acetylaminofluorene is a three-ring PAH arylamide carcinogen.
[c]Air carbonaceous particles, especially particulate matter < 2.5 are vectors of chemicals, including PAHs and organochlorines (pesticides).
[d]Include AAs and HAAs.
[e]Such as di(2-ethylhexyl) phthalate and butyl benzyl phthalate.
[f]Prolactin, estrogens, androgens and others.
[g]Nitrates, nitrites, nitrosamines and nitrosamides.
[h]Include organochlorines such as dioxins and PCBs.
[i]PAHs of high molecular weight (five to seven rings), such as B[*a*]P, are promoters, but they also induce DNA adduction processes and thus are mutagenic, whereas PAHs with low molecular weight (three to four rings), such as phenanthrene and pyrene, are non-genotoxic promoters (73).
[j]Include organochlorines, carbamates, pyretroids and other pesticides. They may act as endocrine disruptors or immunosuppressors (promoters), but some of them can be also mutagenic.

Table III. Some categories of pharmaceuticals and cosmetics with presumed or proved carcinogenic properties in humans

Anticancer drugs	Anti-estrogens	Endometrium carcinoma
	Alkylating agents	Leukemia, lymphoma, sarcoma, breast cancer and other solid tumors
	Others	—
Common pharmaceuticals	Oral contraceptives	Breast cancer
	Hormone replacement therapy	Breast cancer
	Cholesterol-lowering drugs[a]	—
	Other medicines[a]	—
Cosmetics	AAs (hair dyes)	Bladder cancer
	Parabens	Breast cancer

[a]Carcinogenic in the 2 year rodent carcinogenesis bioassay, but not proved to be carcinogenic in humans (59).

However, during metabolization, procarcinogens may be unexpectedly transformed into active carcinogens, a bioactivation process that refers to cocarcinogenesis. A typical example is B[*a*]P, which is not carcinogenic as such but first metabolically activated by CYP1A1 and CYP1B1 to yield B[*a*]P-7,8 dihydroepoxide, a metabolite further hydrolized by the microsomal epoxide hydrolase (EPHX1) to (F)-B[*a*]P-trans-7,8-dihydrodiol, before conversion by CYP1B1 into the most highly ROI B[*a*]P-7,8-dihydrodiol-9,10-epoxide, which forms stable DNA adducts and so is mutagenic and carcinogenic (81,82).

As evidenced from experiments on skin carcinogenesis using knockout mice deficient in NAD(P)H:quinone oxidoreductase-1 (NQO1) activity (NQO1−/−), a striking point is that the tumorigenic effect of B[*a*]P is enhanced in the NQO1−/− mice in comparison with their wild NQO1+/+ counterparts. This finding suggests that NQO1, a flavoprotein which catalyzes a one-electron reduction of quinones and thus contribute to their metabolic detoxification, may inhibit the cocarcinogenic bioactivation of electrophiles such as B[*a*]P and protect the organism against PAH mutagenicity and carcinogenicity by inhibiting quinone-induced oxidative stress (83). However, because under specific circumstances NQO1-associated metabolism may yield reactive oxygen species (ROS) or contribute to generate alkylating species (84), NQO1 might in fact exert either beneficial or harmful effects.

The theory of soft and hard electrophiles. As initially conceptualized by Pullman *et al.* (85), then by Miller *et al.* (86), a basic general mechanism of bioactivation of procarcinogens has been put forward pointing out that a parent molecule—generally a 'soft' electrophile—may be converted into an oxidative metabolite, which is a 'hard' electrophile, so the parent molecule and its oxidative metabolite, because they are associated with a distinct electrophilic capacity, may exhibit or not carcinogenic properties. A typical example that illustrates this theory is the ECC acrylonitrile (87,88). The vinyl group of acrylonitrile is a soft electrophilic center that reacts in a reversible manner with the free sulfhydril groups of GSH- and sulfhydril-containing proteins. In contrast, metabolic epoxidation of the double bond of acrylonitrile produces the relatively hard electrophilic metabolite, cyanoethylene oxide, which can irreversibly adduct DNA and thus may be mutagenic and carcinogenic (89). The difference in electrophilicity might therefore account for the different nucleophilic target between a parent molecule and its metabolite and finally predict whether a molecule can form stable DNA adducts and be mutagenic (90,91). However, whether this molecular mechanism allows distinguishing exogenous chemicals from endogenous molecules for their carcinogenic potential needs further investigation.

The role of phase I and phase II enzymes in the detoxification or activation process. Among phase I XMEs that are capable of either detoxification or metabolic activation of procarcinogens are monooxydases of the CYP system that represent 70–80% of all phase I XMEs and other procarcinogen-activating inducible XMEs, including oxidoreductases, EPHXs such as EPHX1 and peroxidases such as myeloperoxidase (MPO) (Table IV). The CYP system, which comprises >40 isoforms, can either metabolically detoxify or activate numerous ECCs such as PAHs, nitrosamines and other NOCs and arylamines such as AAs and HAAs. Among the CYP enzymes, those of the CYP1, CYP2, CYP3 and CYP4 gene families—more particularly CYP1 and CYP2—are XMEs most directly involved in exogenous chemical carcinogenesis, whereas enzymes in the other CYP gene families, because they act on endogenous substrates (e.g. sex steroids, coticosteroids, bile acids or retinoic acids), may be involved in endogenous tumor promotion. Many substrates of the CYP1 enzymes are AhR coplanar ligands and among the different CYP1 isoforms

Table IV. Main phase I and phase II enzymes and other proteins involved in the metabolism of xenobiotics

	Phase I XMEs	Phase II XMEs	Non-enzymatic proteins:
Function	Functionalization (activation or inhibition)	Conjugation[a]	Conjugating proteins:
Role	Introduce or reveal a chemical function	Add a very soluble grouping	• GSH
Implicated molecules	Oxidation	UGTs	ABC efflux pump transporters:
	CYP-dependent monooxygenases	GSTs	• MDR-1/ABCB1 (P-gp)
	Xanthine oxidase	SULTs	• MRP2/ABCC2
	Peroxidases	EPHXs	
	Amine oxidases	MTs	
	Monoamine oxidases	NAT	
	Dioxygenases	NQO1	
	Cyclooxygenases	Transaminases	
	Reduction		
	CYP-dependent reductases		
	Reductases		
	Aldoketoreductases		
	GSH peroxidase		
	Hydrolysis		
	Epoxide hydrolases		
	Hydrolases		
	Esterases		
	Carboxylesterases,		
	Sulfatases		
	Amidases		
	Others		
	NAD-dependent and NADP-dependent alcohol dehydrogenases		
	NAD-dependent and NADP-dependent aldehyde dehydrogenases		
	NAD-dependent and NADP-dependent steroid dehydrogenases		
	Superoxide dismutase		

This categorization into phase I and phase II classes is not rigid. Some enzymes can be classified as either phase I or phase II. UGTs, UDP-glucuronosyl transferases; SULTs, sulfotransferases; MTs, methyltransferases; MDR-1, multi-drug resistance transporter 1; MRP2, multi-drug resistance-associated protein 2.
[a]A deconjugation process involving phase II enzymes and other endogenous molecules may regenerate phase I products.

there is some degree of substrate specificity. For example, whereas CYP1A2 only handles HAAs such as 4-amino biphenyl, aminoazodyes or foodborne HAAs, CYP1A1 and CYP1B1 induction mostly contributes to the metabolization and activation of PAHs and PHAHs (34). Despite the fact that the carcinogenic activation of both LPAHs and HPAHs mainly depends on the induction of CYP1A1 and CYP1B1, they, however, differ fundamentally in that LPAHs, such as pyrene and phenanthrene, are metabolized into ROIs that cannot adduct DNA and thus are not mutagenic, but only tumor promoters, whereas HPAHs, such as B[*a*]P, 3-methylchloranthrene and dimethylbenzanthracene, because they yield ROIs stably adducting DNA, are not only tumor promoters but also mutagenic carcinogens (92).

Induction of the multiple isoforms of peroxidases and especially of MPO, an ubiquitus lysosomal enzyme that is induced during inflammation, may lead not only to the production of free radicals (93) but also to the metabolic activation of B[*a*]P (94) and AAs (95).

As outlined previously, this suggests that inflammation may play a central role in exogenous chemical carcinogenesis not only by contributing to tumor promotion but also by inducing tumor initiation through cocarcinogenic effects. Induction of EPHX1, which hydrolyzes to dihydrodiols many ROIs such as arene, alkene and aliphatic epoxides generated by the CYP system and other phase I XMEs, may in fact play a dual role by either detoxifying or bioactivating PAHs and other pollutants depending on the substrate (96).

Likewise, phase II-conjugating enzymes such as UDP-glucuronyl transferases, GSH-*S*-transferases (GSTs), *N*-acetyl transferases (NAT) and sulfotransferases, although being generally protective, may paradoxically be procarcinogen-activating inducible enzymes (97).

In an attempt at manipulating enzyme induction to gain clinically specific protective anticancer effects, a distinction between phase I and phase II enzymes has, however, been proposed based on the fact that phase I XMEs such as CYP1 appeared to be mostly involved in carcinogenic activation, whereas phase II XMEs, such as UDP-glucuronyl transferases, GSTs, EPHX1 and NQO1 [the latter enzyme being generally considered as a representative enzymatic marker for protection (98)] were postulated to mostly catalyze detoxification (99). On the basis of this distinction, phase II enzymes have thus been hypothesized to be a primary line of defense against electrophiles and consequently several families of phase II inducers, including isothiocyanates such as sulforaphane, have been so far proposed for anticancer chemoprevention (100).

However, the strategy of inducing phase II enzymes for chemoprevention was already in place before 1980 (101) and despite improvement in knowledge about the effects of conjugating enzymes (102–104) current progresses did not appear sufficient to be clinically relevant. This might be due to a lack of correlation between the results obtained from the *in vitro* tests and from the *in vivo* situation since it is believed that in all tissues where the detoxification process takes place obtaining detoxification rather than toxicity needs that the action of phase I enzymes such as CYP1A1 and CYP1A2 must be tightly coupled to that of phase II-conjugating enzymes. Consequently, any absence of or loose coupling to phase II enzymes might result in enhanced adduct formation and oxidative stress, suggesting that the *in vivo* situation is certainly much more complex than the *in vitro* observations (34). Indeed, in the intact animal, the role of CYP1 enzymes in detoxification versus metabolic activation would in fact depend on their tissular content and location, the amount of phase II enzymes and the degree of coupling to phase II enzymes, whereas at the organism level, it would further depend on route of administration and target organs of ECCs (40).

In addition to phase I and to phase II XMEs, ABC transporters including the multi-drug resistance transporter 1 and multi-drug resistance-associated protein 2 (now termed ABCB1 and ABCC2, respectively) may play an important role in the cellular defense by mediating cellular efflux of xenobiotics, but this needs to be precised.

The contributing role of endogenous bacteria. Endogenous bacteria may also contribute to activating procarcinogens into carcinogens. This is the case for AAs, for which the glucuruno conjugate CYP1A2-induced hydroxylamine is deconjugated in the colon by a bacterial glucuronidase, so hydroxylamine can be acetylated by NAT2. This concerns also NOCs (105). Nitrates are not *per se* carcinogenic but can be transformed into nitrites through nitrosation by the bacterial microflora of the digestive tract, thereby nitrites can be transformed into highly mutagenic NOCs such as alkylnitrosamines and alkylnitrosamides (106), which may be further activated by CYP2E1, CYP2A6 and CYP2D6 to form stable DNA adducts in target tissues.

Why the AhR-activating and the CYP-inducible systems play a central role in exogenous chemical carcinogenesis. A number of exogenous chemicals that cause cancer in laboratory animals are not directly mutagenic or demonstrably mutagenic (107,108) but have been shown to act as tumor promoters and/or cocarcinogens. These xenochemicals mainly include LPAHs and PHAHs such as dioxins, PCBs and several organochlorine pesticides. As indicated previously, a basic property of coplanar aromatic organic pollutants such as LPAHs, HPAHs and PHAHs is that they act through a common intracellular ubiquitous molecular pathway involving the AhR. AhR is a member of the basic helix-loop-helix/Per-AhR nuclear translocator (Arnt)-Sim gene family of transcription factors (109) that mediates the pleiotropic phenotypic effects of a large group of both natural and synthetic aromatic organic molecules such as those pollutants (33,110,111). Upon binding to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the liganted AhR translocates to the nucleus where it switches its partner molecule from intracytoplasmic heat shock protein 90 kD to Arnt protein, thus leading the AhR–Arnt heterodimeric complex to bind to the xenobiotic response elements sequence in the promoter region of target genes (112) to activate their expression. Ligands that combine with and activate AhR therefore activate the transcription of many target genes that encode for the three CYP1 genes, but they also independently activate genes that control complex cellular responses such as cell proliferation, cell cycle regulation and apoptosis. Consequently, AhR activation may induce a broad spectrum of systemic promoting and cocarcinogenic effects. This is the case for dioxins and PCBs, which mainly act as tumor promoters (113). This is also the case for PAHs, since AhR activation triggers the induction of CYP1 phase I XMEs (114,115) and consequently the cocarcinogenic activation of LPAHs into tumor promoters and of HPAHs into tumor promoters and mutagens.

In addition, activation of CYP genes such as CYP1A1 can generate free radicals through the induction of oxidative stress (116) and this process might explain why dioxins and PCBs in addition to their promoting effects may be mutagenic (117,118). However, the mechanism by which AhR activation may result either in carcinogenic or protective effects is not clear since following AhR activation, in addition to phase I XMEs, phase II XMEs such as UDP-glucuronyl transferases, GSTs and NQO1 may also be induced (112). Moreover, many intracellular interactions of AhR and Arnt with various regulatory transcription factors such as retinoblastoma protein-1 (119), NF-κB (120), estrogen receptor α (121) and SP1 and with different coactivators and repressors may modify the transcriptional activity of the AhR–Arnt heterodimeric complex (112), and this might explain why chemicals that bind to AhR may elicit detoxification agonist or antagonist responses (122).

Moreover, there are wide inter- and intraspecies differences in sensitivity to toxicological responses to AhR ligands (123) and it has been shown that differences in AhR sensitivity between inbred mouse strains may be correlated with variations in CYP1 inducibility, thus with differences in risk of toxicity and cancer caused by PAHs and arylamines. An interesting observation is the correlation of AhR sensitivity and CYP1 inducibility with the site of tumor formation (124). When PAHs are administered in contact with target organ of mice with high AhR sensitivity, these mice are at higher risk to develop local PAH-induced mutagenesis and cancer than mice with poor AhR sensitivity, whereas when PAHs are administered at distance of target organ in mice with poor AhR sensitivity, these mice are at higher risk

of general PAH-induced malignancy and toxicity (33,124). This apparently paradoxal observation has received some explanation. Whereas in the first case, local occurrence of cancer may be interpreted as resulting from direct intracellular AhR activation and subsequent CYP1 induction by PAHs, in the second case it may be due to direct CYP1 induction in the liver and other tissue after PAH first pass elimination kinetics. AhR activation may thus contribute to exogenous chemical carcinogenesis via three major mechanisms: activating procarcinogens such as PAHs into carcinogens through CYP1 cocarcinogenic induction; mediating tumor promotion of PAHs and PHAHs through the activation of genes involved in cell proliferation, cell cycle regulation and apoptosis and finally affecting the site of PAH-induced tumor formation.

To sum up, because following AhR activation the CYP system is a major determinant for the activation of many exogenous organic procarcinogens, both widespread systems appear to be central for exogenous chemical carcinogenesis. This concept appears as much justified as the so-called CYP1–AhR loop paradigm (34) accounts not only for the promoting or cocarcinogenic effects of many organic environmental pollutants but also for the mutagenic effects of several of them.

Molecular mechanisms of mutagenesis and carcinogenesis by exogenous chemicals

Chemicals can induce mutations through DNA adduction and oxidative DNA damage through free-radical production. They can also induce indirect mutagenesis through aberrant epigenetic changes. DNA adduction is the best recognized genomic stress-induced mechanism by which many exogenous organic chemical mutagens such as HPAHs, NOCs, AAs and HAAs have been proved to induce cancer (4). Because the carcinogenic mechanism of non-organic exogenous chemicals such as metals and metalloids is more complex, we analyze them separately.

DNA adduction, reparation and mutagenicity. During tumor initiation and promotion, cells are usually able to elicit an activated DNA damage response to genomic stress, but as for a long time, the carcinogenic process is progressing, this response is not sufficient to avoid cancer occurrence (125). ECCs can generate a wide variety of DNA damage ranging from small adducts to cross-link lesions and double-strand breaks (DSBs). A major basic and specific property of ECCs that may distinguish them from endogenous carcinogenic molecules is their ability to induce stable and irreversible adducts—i.e. covalent bonds with macromolecules (126,127)—and that all DNA adducts they form cannot be correctly repaired by the cell repair systems (41,128,129).

A further argument supporting the hypothesis that ECCs may play a major role in carcinogenesis comes from the fact that ROIs appear to be more often derived from exogenous chemicals than from endogenous natural substrates (34). In response to chemically induced genomic stress, an extended molecular complex involving recognition factors, protein kinases and transcription factors such as the tumor-suppressor protein p53 (18) and the cyclin-dependent kinase inhibitor p21 (130) that mediates p53-dependent G_1 growth arrest is activated to signal DNA damage, arrest cell cycle at specific check points and either repair DNA lesions or initiate apoptosis. Small chemical DNA adducts may be commonly repaired by direct reversal or by the base excision repair system, whereas bulky chemical adducts or single-strand break lesions, because they usually obstruct DNA transcription and replication, activate the nucleotide excision repair system and also the mismatch repair system, which can specifically recognize and remove structural DNA distortion occurring during replication. However, for bulky adducts and single-strand break lesions and as much as for more important DNA alterations such as DSBs and interstrand cross-links, it is anticipated that no correction procedure associated with the reparation process is error free. Indeed, despite the action of the excision repair cross-complementary protein 1 that, as part of a specific nuclease complex, is involved in repair of bulky adducts and interstrand cross-links and of X-ray repair cross-complementary protein 1 that, as part of a complex molecular process, tentatively tends to repair DSBs and interstrand cross-links by using the homologous or non-homologous end-joining recombination pathways, uncorrect repair and consequently mutations can occur in non-apoptotic cells.

As outlined above, a possible explanation for the unfaithful reparation of DNA alterations induced by ECCs or their ROIs is that many of them are ‘hard’ electrophiles that irreversibly adduct hard nucleophilic sites on DNA, whereas polar (hydrophilic) endogenous molecules such as unsaturated aldehydes and ketones are ‘soft’ electrophiles that usually reversibly react with soft nucleophiles on the DNA (85,86). Because there is a good correlation between the ability to form stable DNA adducts and the capacity to induce tumors in animals, DNA is considered as the ultimate target for most chemical carcinogens (131). This is indeed also the case for human cancers, since there is a positive correlation between DNA adduct levels and mutagenicity in human cell cultures (132,133) and between *in vivo* detection of DNA adducts in cell tissues and cancer occurrence for many cancer types such as lung (134,135), breast (136), colon (137), small intestine (138) and pancreas cancers (139), suggesting that many human cancers of apparently unknown origin are in fact caused by chemicals.

Mutagenicity and carcinogenicity. Many experiments have elucidated the overall mechanism of DNA adduction by chemicals. *In vitro*, DNA adduct formation is dose dependent. For many chemicals, the dose–response relationship is initially linear with no threshold, meaning that low doses rather than cytotoxic high doses of exogenous carcinogens are mutagenic. However, albeit the detection of DNA adduct does not necessarily mean the induction of mutations, the frequent positive correlation of the predominant mutation hot spots with the major DNA adducts formed strongly suggests a causal role of chemically induced DNA adducts in mutagenesis (140). Because the interaction of genotoxic carcinogens with DNA has been thought not to be random (127,141), it has been hypothesized that ECCs could induce some specific and reproducible mutations. However, because it has been shown that ECCs may in fact induce various types of mutations depending on the conformation of DNA, the type and the location of the adducts, the ‘fingerprint’ hypothesis has not been confirmed.

As aforementioned, a basic property that makes ECCs or their ROIs more prone than natural endogenous molecules to induce chromosome breaks and large deletions, thereby aneuploidy (142), is the bulky adducts they form when bound to double-strand DNA and the lack of forthright repair due to considerable DNA conformation and functional changes (4). Structural analysis of bulky adducts has particularly been done for B[*a*]P, for which the bulky benzo[*a*]pyrene-7,8-diol-9,10-epoxide residue lies in the minor grove of the DNA helix, and for the AA *N*-2-acetyl aminofluorene, for which the bulky C8-(2-acetylaminofluorene)-guanine 2 *N*-2-acetyl aminofluorene residue induces major conformational change in DNA and mutations consisting in base displacement and alterations of genomic sequences (143).

However, since DNA adducts are detected, irrespective of whether they cause cancer, adduct levels are considered indicators of exposure, but not necessarily of mutagenesis and carcinogenesis (144,145). In a serial analysis of chemicals tested for their mutagenicity and carcinogenicity, 66% of non-carcinogens were found to be mutagenic, whereas 16% of tested carcinogens were not found to be mutagenic (146). This strongly supports the concept according to which carcinogenicity is more than mutagenicity (14). Nevertheless, the multiple ways whereby many exogenous chemicals can irreversibly adduct DNA and induce conformational and functional DNA changes make them potentially important causes of cancer and DNA adduction presumably a major contributing mechanism of chemical carcinogenesis.

Free-radical production. Free-radical production is also a related proposed mechanism of chemically induced carcinogenesis. A major function of mitochondria is to link the energy-releasing activities of

electron transport and proton pumping with the energy conserving process of oxidative phosphorylation in order to transform the energetic potential of food into ATP. However, side reactions of the mitochondrial electron transport chain with molecular oxygen generate ROS (147). In addition, reactive nitrogen species (RNS) such as nitric oxide (148) can be formed during inflammation by macrophages and other phagocyting cells (149). In normal redox conditions, there are many enzymes such as superoxide dismutase (150,151), catalases, NQO1 and heme oxgygenases that together with redox protein couples play a key role in free-radical detoxification to maintain the redox state in the cell environment. The GSH–disulfide GSH couple (GSH–disulfide GSH/2GSH) in particular is an important indicator of redox cell potential (152).

Oxidative stress has classically been viewed as a stochastic process of cell damage and antioxidants, simply as free-radical scavengers. Only recently, it has been recognized that free radicals such as ROS and RNS act as secondary messengers in intracellular signaling cascades and thereby may contribute to cell-promoting effects at physiological concentrations (153–155). Indeed, as indicated previously, changes in the intracellular redox state trigger the activation of the immediate early response genes c-fos and c-jun and consequently the activation of stress response transcription factors such as AP-1 and NF-κB, which regulate the expression of a variety of downstream target genes (156). Pro-oxidant states have therefore been considered to be associated with tumor promotion (157) and oxidative stress to possibly cause cancer. It has been shown that oxidative DNA lesions resulting from exposure to chemical carcinogens might cause mispairings and consequently inheritable mutations (158) and that many chemical tumor promoters might affect gene expression through perturbation of a GSH-dependent signal transduction pathway (159,160), as a result of oxidation of lipids and proteins and more precisely as a consequence of protein kinase C activation and of inhibition of GJIC (160). Because many exogenous chemicals can directly or indirectly generate ROS, it has therefore been proposed that free-radical production may also play an important contributing role in carcinogenesis through indirect mutagenesis and promotion induction. However, as indicated in Figure 1, there is presumably a dose-dependent relationship between the local production of free radicals and their biological effects, so at low concentrations cell-promoting effects may predominate, whereas at higher concentrations (when the redox potential of the system—i.e. the redox buffering capacity of cells—is saturated by an excess of ROS and/or RNS), ROS and/or RNS can damage macromolecules, induce oxidative DNA lesions and finally induce cell death at the highest concentrations (161).

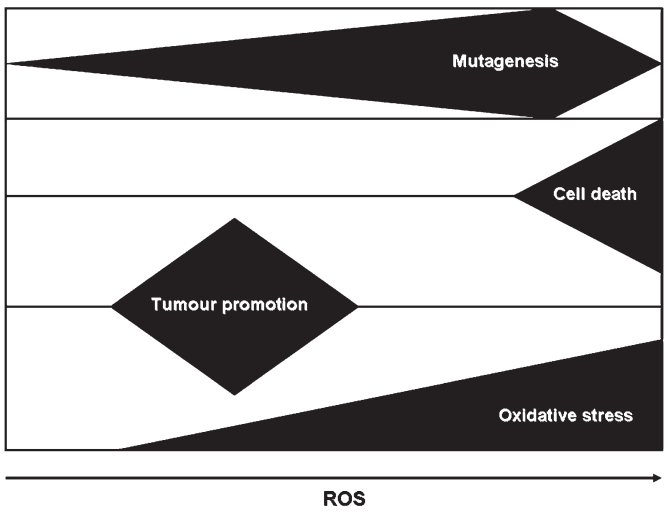

Fig. 1. Representation of a dose-dependent hypothetic relationship between oxygen-free radicals and cancer genesis according to Dreher and Junod (161). Local doses of free radicals capable of cancer genesis are infratoxic. Doses capable of inducing promotion are lower than those inducing mutagenesis.

As indicated previously, a common interpretation of the carcinogenic role of chronic inflammation is basically free-radical production (162). Moreover, cigarette smoke, air pollutants such as traffic exhausts and industrial chemicals are by themselves major sources of ROS that can damage the organism following inhalation. Also a large number of environmental carcinogens have been shown to generate and produce ROS as by-products of their *in vivo* metabolism. They include PHAHs, such as dioxins and dioxin-like PCBs (118,163), solvents such as trichloroethylene (164), organochlorine pesticides such as dichloro-diphenyl-trichloroethane (165) and quinonoid compounds, such as the herbicide paraquat (166), which has been proved to block GJIC in isolated mouse hepatocytes (167) and thus to possibly contribute to carcinogenesis by this mechanism. Among ECCs thought to be genotoxic and carcinogenic through free-radical production are the prototypical examples of dioxins and dioxin-like PCBs (117).

Evidence of intracellular oxidative stress in the whole organism is, however, not sufficient to causally correlate free-radical production with local occurrence of cancer (168). Moreover, *in vitro* and *in vivo* induction of intrachromosomal rearrangements and mutations—as it is the case for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and dioxin-like PCBs (117)—is a prerequisite before assessing free radicals to cause cancer through mutagenesis. Finally, because the mutagenic and carcinogenic effects of free radicals may depend on their intracellular concentration, we believe that implication of free radicals in carcinogenesis needs to be soundly established before assuming a causal relationship.

Epigenetic changes and indirect mutagenesis. ECCs do not only contribute to direct mutagenesis by adducting to DNA. They can also modify molecular metabolic pathways and cell signals generally by altering protein, RNA and protein expression, hence inducing epigenetic changes and therefore contributing to indirect mutagenesis (169). A prototypical example is DNA methylation alteration. In a recent study carried out in people exposed to low-level benzene emitted from traffic exhaust fumes, it was observed that normal tissues exhibit DNA methylation alterations similar to those consistently found in acute myeloid leukemia and other malignancies (170). This important observation strongly suggests that low-dose chronic exposure to widespread airborne pollutants such as benzene may induce indirect mutagenesis through epigenetic changes and thus may contribute to carcinogenesis.

Metals and metalloids. In addition to exogenous organic chemicals, several metals and metalloids have been rated as certain or probable carcinogens by International Agency for Research on Cancer (171), albeit their mechanism of action is far less clear. Metals and metalloids could act as cocarcinogens by activating procarcinogens in the liver (172,173) or by increasing the promoting effect of endogenous steroid hormones such as estrogens (174). They could also act by replacing the natural enzyme-associated metal, thus inactivating the activities of key protective enzymes. For example, carcinogenic metals and metalloids, e.g. arsenic, cadmium and nickel, and some putative carcinogens such as cobalt and lead can inhibit zinc finger-containing DNA repair proteins. Damage of zinc finger in DNA repair proteins can therefore be regarded as a novel mechanism in carcinogenesis (175). Other mechanisms of metal mutagenesis include interaction with DNA. Chromium(VI) is taken up by cells as chromate anions and is reduced intracellularly via reactive intermediates to stable Cr(III), which can directly adduct DNA. These Cr(III) intermediates may affect DNA by terminating replication or reducing replication fidelity, thus leading to mutations (176,177). Cr(III) can also form DNA–proteins and DNA–amino acids and GSH cross-links (178,179). Platinum compounds such as *cis*-diaminedichloroplatinum are well-known anticancer therapeutic agents. At low dose, they can form DNA cross-link and DNA–protein cross-link causing mutations

(180,181), whereas at higher dose, they are cytotoxic and thus acquire anticancer properties. Nickel may act via an epigenetic mechanism involving heterochromatic regions of the genome (182). The mechanism of arsenic-induced carcinogenesis is multifactorial and still unclear. The current concept is that it may act as tumor promoter through activation of AP-1 and NF-κB following ROS overproduction (183) and/or oversecretion of pro-inflammatory and growth-promoting cytokines (184). However, arsenic might also be indirectly mutagenic through epigenic mechanisms involving DNA hypomethylation caused by methyl depletion, since arsenic needs to be continuously methylated for detoxification (185). Many studies have focused on metal-induced carcinogenicity, emphasizing the mutagenic role of metals such as iron, copper, chromium, nickel, cadmium and arsenic in carcinogenesis through the production of ROS. Metal-mediated formation of free radicals may cause various modifications of DNA and intracellular molecular changes that could contribute to carcinogenesis. A typical example is asbestos-induced cancers that may in fact be mainly caused by the generation of free radicals due to the presence of oxidative iron in the mineral (186,187).

Genetic susceptibility to exogenous chemical carcinogenesis

From this basic overview, carcinogenesis clearly is a complex multifactorial process. Adding to this complexity, gene–environment interactions involving ECC exposure in relation with host-related gene polymorphisms are elements that provide further difficulties in cancer risk assessment.

Most so far discovered inherited cancer susceptibility genes are highly penetrant, but they are too rare to account for >1% of cancer cases overall (188). In contrast, there is increasing evidence that sporadic cancer may arise in a large proportion of individuals who carry polymorphic low-penetrance inherited cancer susceptibility genes (189). Although these genes do not cause high enough risk to result in large multiple-case cancer families to allow gene identification by conventional linkage techniques, analyzing single-nucleotide polymorphisms (SNPs) via DNA microarray assays and collecting data obtained from the analysis of the entire human genome suggest that polygenic mechanisms (involving the combined effect of numerous beneficial and harmful polymorphic allelic variants), rather than mutations in a few specific genes, are likely to account for overall inherited genetic susceptibility of patients undergoing exogenous chemical carcinogenesis (190). This polygenic model makes carcinogenesis an extremely complex process indeed, as it involves not only multiple host-related cellular systems regulated by many genes (191) but also interindividual variations of cancer susceptibility due to genetic polymorphisms. However, genetic polymorphisms are only effect contributors, meaning that without exogenous chemical exposure they have no effect. Moreover, the observed effects depend not only on gene dosage (for example homozygosity for the mutated allele is associated with a significantly higher risk than heterozygosity) but also on dose intensity of chemical exposure (192) and of course on exposure during development.

Since a seminal work of Harris *et al.* (193) showing interindividual variations in carcinogen activation, it has been thought that efficacy of host defense mechanisms against external exposure to chemicals mainly depends on a set of polymorphic allelic variants of genes encoding for XMEs or for other proteins involved in xenobiotic detoxification or DNA repair. As indicated in Table V, polymorphic variants involved in exogenous chemical carcinogenesis may concern not only genes coding for phase I and phase II XMEs and DNA repair proteins (194) but also genes involved in cell cycle control. Phase I and II XME polymorphic allelic variants generally lead intermediate or poor metabolism phenotypes, hence to low or no enzyme activity (195), whereas inherited amplification of XME-coding genes may result in fast metabolization phenotypes that activate or inactivate ECCs (196) depending on the type of enzymatic substrates and of metabolic pathways. Several studies have found correlations between exogenous chemical exposure, phase I or phase II XME expression, genetic polymorphisms and cancer risk.

Table V. Some candidates of polymorphic susceptibility genes that may influence exogenous chemical carcinogenesis in humans

Type of gene	Gene
Phase I polymorphisms	*CYP1A1*, *CYP1A2*, *CYP2A6*, *CYP1B1*, *CYP2D6*, *CYP2E1*, *CYP3A4*, *MPO*, *EPHX1*
Phase II polymorphisms	*GSTM1*, *GSTT1*, *GSTP1*, *NAT1*, *NAT2*, *NQO1*, *SULT1A1*, *SOD2*
ABC polymorphisms	*MRP2/ABCC2*
DNA repair genes	*XRCC1*, *XRCC3*, *XPD*, *XPF*, *ERCC1*
Cell cycle control genes	*TP53*, *HRAS*

SULT1A1, sulfotransferase 1A1; *SOD2*, superoxide dismutase 2; *MRP2*, multi-drug resistance-associated protein 2; *ABCC2*, ATP-binding cassette sub-family C, member 2; *XRCC1*, X-ray repair complementing defective repair in Chinese hamster cells 1; *XPD*, xeroderma pigmentosum D; *ERCC1*, excision repair cross-complementing rodent repair deficiency, complementation group 1.

A previous review of molecular epidemiology studies analyzing the role of exposure to ECCs pointed out that increased DNA adduct levels and chromosomal aberration levels mostly correlated with CYP1A1, GSTM1 and NAT2 polymorphisms (197). In fact genetic polymorphisms concern a larger series of genes, expression of these genes mainly depend on the type and dose intensity of exogenous chemical exposure (157,198), there may be a considerable number of SNP variants for each gene (there are, for example 118 and 178 identified SNP variants for the EPHX1 gene and for the CYP1B1 gene, respectively) and finally a wide range of human cancers are concerned by genetic polymorphisms (199,200). As indicated in Table V, polymorphisms of genes coding for phase I XMEs do not only address the three types of CYP1 genes but also CYP2, CYP3 and CYP4 genes. For example, an increased risk of lung cancer has been reported to correlate not only with variants of the CYP1A1 gene (201) but also with variants of the CYP2D6 (202) and CYP3A1 genes and with variants of the CYP3A4 gene that play a pivotal role in the metabolism of numerous xenobiotics such as PAHs and NOCs (203). Also an increased risk of lung, head and neck, esophage and stomach cancers have been reported to be associated with variants of the CYP2E1 (204), CYP2A6 and CYP3A1 genes (203) in tobacco smokers and more generally in people exposed to nitrosamines. Likewise, an increased risk of breast cancer has been found to correlate with variants of the CYP1A1 (205) and/or CYP1B1 genes (206) and in women exposed to environmental PHAHs such as dioxins and organochlorine pesticides.

In addition, polymorphisms of genes coding for phase I XMEs other than CYP, such as EPHX1 and MPO, as well as polymorphisms of genes coding for phase II XMEs such as NQO1, NAT1 and NAT2, GSTM1, GSTT1 and GSTP1 have been correlated with cancer risk for many cancers such as lung, breast, head and neck, liver, bladder and colon cancers. For example, two haplotypes in the EPHX1 genes have been recently identified and shown to be significantly associated with lung cancer risk (207), whereas in tobacco smokers, polymorphisms of the MPO-463A gene revealed paradoxal with protective (208) or no protective effects (209). A similar paradoxal feature might hold true for NQO1, since, as reported above, on the basis of knockout mouse experiments NQO1 is thought to induce some protective anticancer effect, whereas, for example the association of NQO1 and GSTP1 polymorphisms increases the risk of head and neck cancers in tobacco smokers (210). Moreover, a phenotype of slow or fast metabolic activation may lead to different cancer types. This is the case for NAT polymorphisms. A genotypically recessive slow acetylation phenotype involving NAT1 has been found to be associated with occupationally induced bladder cancer in dye workers exposed to AAs (211), whereas a genotypically dominant rapid acetylator phenotype, involving both NAT1 and NAT2, has been found to be associated with colon cancer in people exposed to dietary HAAs (212). Also, it has been shown that combining the fast acetylation NAT2 phenotype with a fast

CYP1A2 phenotype increases the risk of colon cancer in people exposed to foodborne HAAs (213).

Several studies have recently provided data about a possible association of polymorphic variants of the ABCC2 gene with an increased risk of hepatocellular carcinoma and cholangiocarcinoma, but these data need confirmation. Many SNPs have been described in DNA repair genes, suggesting that DNA repair processes may be affected by a high degree of genetic variation and could be highly involved in interindividual cancer susceptibility (214). There is indeed a markedly increased cancer risk associated with reduced phenotypic DNA repair capacity (194,214,215) with considerable enhancement of this risk by specific combinations of polymorphic allelic variants of genes coding for the different repair proteins involved in base excision repair, such as X-ray repair cross-complementary protein 1 and PAE1, in nucleotide excision repair, such as XPD and XPA, and in DSB repair, such as XRCC3. Such deficient repair capacities have been correlated with increased lung cancer risk (203) and X-ray repair cross-complementary protein 1 polymorphisms have been shown to influence breast cancer risk (216).

Also, p53 polymorphisms have been described but only a small fraction, if any of the >200 SNPs so far identified is presently hypothesized to cause measurable inherited phenotypic perturbations in the population (217), but evidence for elevated risk of both breast and lung cancer with inheritance of rare H-ras-1 alleles has been provided from a meta-analysis of case–control studies (218).

Despite the difficult challenge aiming to identify metabolizing, repair and cell cycle polymorphisms in genes involved in exogenous chemical carcinogenesis, using adequate methodology studies may help to further pinpoint the mechanisms of action of ECCs and may further genetics-based screening and prophylactic therapy (219).

Conclusion

Identifying the causes of cancer would have considerable public health consequences ranging from primary prevention to screening, early diagnosis and treatment. Because many exogenous chemicals are lipophilic, bioaccumulate in the adipose tissue, metabolize into DNA-reactive by-products, form stable and bulky DNA adducts, induce free radicals and/or act through epigenic mechanisms and, consequently, due to all these properties, can be highly mutagenic through direct or indirect mechanisms, we believe that they may be major contributors to chemical carcinogenesis in humans.

This ECC hypothesis is indeed fully demonstrated for active tobacco smoking, and it is strongly suggested for passive tobacco smoking, both mixes of many pollutants. The hypothesis is also evidenced for cancers caused by occupational chemical pollution. That could be the same for the ubiquitous environmental chemical carcinogens that pollute the general population, but definitive proof is still lacking.

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