13 Lung Cancer: Mechanisms and Markers—Carcinogens Other Than Asbestos

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Introduction

Inhaled carcinogenic chemicals, mineral fibers and particulates, and carcinogenic metals are the most significant occupational and environmental causes of lung cancer. The gases, fumes, and particulates in industrial environments form complex mixtures, the carcinogenic potential of which may differ from that of each component separately. Particulate matter can absorb chemicals on its surface, which is thought to enhance the deposition of chemicals in the lung, their penetration into lung cells, and carcinogenic action. Personal or involuntary tobacco smoking complicates the exposures even further, since tobacco smoke is also a complex mixture containing carcinogenic agents in chemical and particulate forms.

The carcinogenicity of inhaled substances is influenced not only by their chemical composition, but also by their retention and biopersistence in the lung. The pulmonary deposition and clearance of inhaled particles and fibers are dependent on particle size and dimension. Particles of 10 μm or more in diameter are deposited in the upper airways, whereas those around 1 μm or less in diameter are most effectively retained in the alveolar lung. As an example, inhalation of silver nanoparticles of 20 nm in diameter resulted in a greater lung burden and persistence than larger nanoparticles in animal experiments [1]. Fibrous particles such as asbestos fibers are exceptional in their deposition and clearance, and asbestos fibers up to over 100 μm in length can be found in lung tissue. Inhaled particles and fibers are cleared from the lungs via lymphatics and mucociliary transport. Poorly soluble particles and fibers, which are retained in the lung, form a constant source of toxic damage.

The mechanisms and markers of asbestos carcinogenesis are reviewed in Chaps. 11 and 12. The present Chap. 13 handles pulmonary carcinogens other than asbestos. For more detailed information, the reader is referred to several recent comprehensive reviews cited in this chapter.

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Polycyclic Aromatic Hydrocarbons and Complex Mixtures

Occupational Exposure to Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) arise in the incomplete combustion of fossil and carbonaceous materials and also occur in crude oil deposits. The highest occupational exposures are found in petrochemical industry workers, especially in coke-oven workers, and in workers of metal plants and foundries [2]. Sources of indoor PAH exposure include tobacco smoke, meat and fish roasting and frying, and charcoal grilling in poorly ventilated environments [3]. Examples of occupations with PAH exposure are given in Table 13.1. Workers in the petrochemical industry and in foundries are typically exposed to complex mixtures, in which chemical compounds are bound to metal and mineral particulates of respirable size. Some of these metals and minerals are known or suspected lung carcinogens as such; examples include arsenic, some chromium and nickel compounds, cadmium, vanadium, silica, and fibrous minerals including asbestos. PAH levels and the distribution of different PAH compounds between gaseous and particulate phases have been studied in air samples from foundries. While the gas phase contains on average three times more carcinogenic four- and five-ring PAHs, the total PAH load increases with increasing particle size in individual fractions [4–7].

The distribution of PAHs between gaseous and particulate phases is important because the mechanisms and biomarkers of chemical and particle/fiber carcinogenesis are different. While pure PAH procarcinogens are metabolized via the aryl hydrocarbon receptor (AHR)-mediated pathway to DNA-reactive intermediates, or detoxified and excreted from the

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Table 13.1 Examples of biomarkers of internal dose, biologically effective dose, and early effects in relation to occupational exposures to PAH and complex mixtures

Examples of exposures	Markers of internal dose	Markers of effective dose	Markers of early biological effects
• Involuntary tobacco smoking • Coke-oven workers • Foundry workers • Bitumen workers • Petrochemical industry • Rubber vulcanizing • Diesel exhaust/ working in traffic • Firefighting • Soil remediation • Waste handling	• Urinary metabolites of tobacco constituents – Cotinine (nicotine metabolite) – NNAL and NNAL/cotinine ratio – 1,3-butadiene • Urinary PAH metabolites – 1-hydroxypyrene and other PAH metabolites	• DNA adducts in blood lymphocytes or lung – Bulky DNA adducts – Anti-B[a]PDE-DNA adducts – 8-oxodGuo adducts • Protein adducts – Hemoglobin adducts • Urinary/plasma markers of oxidative DNA damage – Excretion of 8-oxo-7,8-dihydroguanine	• Cytogenetic aberrations detected in blood lymphocyte culture – Micronucleus formation – Sister chromatid exchanges – Chromosomal aberrations • DNA strand breaks in blood lymphocytes (measured by comet assay) • Changes in global and gene-specific promoter methylation • Shorter telomere length

PAH polycyclic aromatic hydrocarbon, *NNAL* tobacco-specific nitrosamine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, *anti-B[a]PDE* anti-benzo[a]pyrene-diol-epoxide, comet assay; alkaline single-cell gel electrophoresis assay

body, particulates, fibers and some metals induce the formation of reactive oxygen (ROS) and nitrogen species (RNS), and oxidative DNA damage. The oxidative stress-induced gene expression is regulated by the transcription factor, nuclear factor erythroid 2-related factor 2 (NRF2). Nevertheless, these two pathways co-operate in many ways, and may potentiate each other in the formation of oxidative DNA damage (e.g., [8]).

Involuntary Tobacco Smoking

Environmental tobacco smoke (ETS) is a significant source of PAH and other tobacco carcinogens for non-smokers in workplaces, especially in poorly ventilated environments. ETS is a complex mixture of gaseous and particulate-bound compounds, including known carcinogens such as acrolein, aromatic amines, acetaldehydes, benzene, cadmium, 1,3-butadiene, tobacco-specific nitrosamines, and polycyclic aromatic hydrocarbons [6, 9, 10]. ETS consists mainly of sidestream smoke emitted from smoldering cigarettes between puffs and to a lesser extent of mainstream smoke exhaled by tobacco smokers [11]. The delivery of different compounds by mainstream and sidestream tobacco smoke is influenced by the efficiency of combustion and differs between tobacco brands due to tobacco blends, ingredients, design, and differences in manufacture. The harmful chemicals in sidestream tobacco smoke are principally responsible for the deleterious health effects of involuntary tobacco smoking. Lodovici et al. studied the PAH content in mainstream and sidestream tobacco smoke from 14 tobacco brands and found that sidestream smoke contained about ten times higher PAH levels than mainstream smoke from most cigarette brands [12]. While the tar content of cigarettes is a good predictor of the release of PAHs in mainstream smoke, PAHs in sidestream smoke do not correlate with tar content [12, 13]. Furthermore, levels of carcinogenic PAH compound benzo[a]pyrene are especially high in sidestream tobacco smoke [12]. Most carcinogenic PAH compounds are present in the particulate phase of tobacco smoke.

The use of electronic cigarettes (e-cigarettes, "vaping") also carries adverse effects on the indoor air quality and exposes the users and non-users to toxic or carcinogenic chemicals. Although the concentrations of many conventional tobacco carcinogens are much lower in e-cigarette aerosols, new harmful chemicals such as formaldehyde and acetaldehyde, are produced from the heating process of glycerol which is one of the main ingredients of e-liquids (see review Zainol Abidin et al. [14]).

Metabolic Activation of PAH Procarcinogens

PAH compounds enter cells as procarcinogens which require metabolic activation to exert their carcinogenic potential. In lung cells PAH compounds bind to a cytoplasmic AH (dioxin) receptor which, after ligand binding, is translocated to the nucleus and dissociates from the cytoplasmic chaperone complex. It then associates with its dimerization partner, ARNT protein, and binds to xenobiotic (dioxin)-responsive elements (XRE) in the promoter (enhancer) regions of AHR-responsive genes, turning on their transcription (for example [15, 16]). AH receptor regulates the transcription of several cytochrome P450 (CYP) enzymes, which are involved in the Phase I metabolism of xenobiotics, and also the transcription of a few Phase II enzymes, including UDP-glucuronosyltransferases 1A1 and 1A6, glutathione S-transferase A2, and NAD(P)H quinone oxidoreductase 1 (NQO1). Generally speaking, Phase I metabolism is responsible for the initial activation step of metabolism, often leading to the formation of reactive intermediates, whereas Phase II metabolism involves the conversion to more polar and water-soluble compounds and detoxification [15, 17].

In the lung, cytochrome P450 enzymes CYP1A1 and CYP1B1, which are under the regulative control of AHR, and epoxide hydrolase catalyze the conversion of PAH procarcinogens to proximate carcinogenic metabolites, PAH-diols, and CYPs further to ultimate carcinogenic metabolites PAH-diol-epoxides.

Reactive metabolites may bind to proteins and DNA, thereby forming adducts, or become detoxified by Phase II enzymes, such as glutathione S-transferases, UDP-glucuronosyltransferases, and sulfotransferases [17, 18]. PAH-diols are also metabolized by aldo-keto reductases (AKR) into reactive PAH *o*-quinones, which are able to form stable and depurinated DNA adducts. The metabolic route catalyzed by AKRs leads to amplified production of ROS ([8], see section Co-carcinogenesis of PAH and inhaled particulates). Furthermore, PAHs are catalyzed by peroxidase activities into radical cations that form depurinated adducts [17, 19–21].

Bulky DNA adducts, which mainly originate from PAH, are considered a measure of internal dose of PAH and if not repaired, may lead to DNA damage. Dennissenko and colleagues mapped the distribution of benzo[a]pyrene diol-epoxide (BPDE) DNA adducts along exons of the *TP53* gene and observed strong and selective adduct formation at guanine positions in codons 157, 248, and 273. These same codons are the mutational hotspots in human lung cancer [22]. Subsequent studies have shown that methylated CpG dinucleotides are the preferential target for BPDE adduct formation and G:C to T:A transversions at *TP53* codons 157, 248, 249, and 273 [23, 24]. The molecular alterations caused by tobacco-derived PAH and occupational PAH exposures are not separable.

Co-carcinogenesis of PAH and Inhaled Particulates

It has long been known in epidemiology that tobacco smoking and asbestos exposure have a synergistic, almost multiplicative effect on lung cancer risk as compared to the risk caused by either exposure alone. The exact mechanisms for the synergism are not known, but the emerging knowledge of the co-operation between the transcription factors and signaling pathways that are induced by PAH procarcinogens and oxidative stress offers a plausible view on co-carcinogenesis. Oxidative stress, together with its effects on cellular structure and function, plays a central role in the carcinogenic process induced by inhaled particulates, including asbestos fibers, silica, and carcinogenic metals, as well as ionizing radiation.

While PAH compounds exert their effects via the AH receptor, which regulates the transcription of a number of xenobiotic-metabolizing enzymes by binding to XRE in the promoters of responsive genes, NRF2 is involved in the regulation of redox homeostasis and controls the antioxidant gene battery via binding to antioxidant responsive elements (ARE) in the regulatory sequences of NRF2-driven genes [25, 26].

Many of the NRF2-regulated genes encode enzymes which are responsible for the detoxification of reactive electrophiles formed by Phase I metabolism by CYPs or for the elimination of reactive oxygen species, including enzymes such as NAD(P)H:quinone oxidoreductase 1 (NQO1), glutathione transferases, UDP-glucuronosyltransferases, aldehyde dehydrogenase, and several antioxidant enzymes [27, 28]. AHR- and NRF2-regulated signaling is coordinated by several mechanisms, for example *AHR* and *NRF2* genes contain each others' binding elements in their regulatory enhancer regions [25]. Furthermore, induction of the expression of a group of genes, such as detoxification enzyme NQO1, requires both AHR and NRF2 [26].

Human aldo-keto reductases AKR1C1, AKR1C2, and AKR1C3 that are under the regulative control of NRF2 catalyze the oxidation of non-K-region PAH *trans*-dihydrodiols to the corresponding *o*-quinones with concomitant production of ROS. The ROS produced can lead to further induction of AKRs, and CYPs via AHR, and amplification of the PAH activation, resulting in the formation of DNA adducts, above all formation of the marker adduct of oxidative DNA damage, namely 8-hydroxyguanine (8-hydroxydeoxyguanosine, 8-OH-G) [8]. Similarly, the ROS produced by particle-induced oxidative stress can potentiate NRF2- and AHR-mediated PAH procarcinogen activation and aggravate the formation of oxidative DNA damage (Fig. 13.1).

The Role of NRF2 in Cancer Promotion

The cytoprotective role of NRF2 as activator of the cellular antioxidant response is long known. It has been shown recently that the constant activation of NRF2 may not be beneficial in all stages of carcinogenesis [29]. The loss of the regulative control of NRF2 in human lung cancer cells may result from several aberrations, such as mutations in the *NRF2* gene or its repressor *KEAP1* (Kelch-like ECH-associated protein 1) [30, 31]. *KEAP1*, which is considered a tumor suppressor, may also be silenced by hypermethylation or the deletion of the chromosomal region 19p [32, 33]. These aberrations, which lead to constant NRF2 activation, may arise as a protective response against reactive electrophiles and oxygen species, or become selected by means of giving a growth advantage and permitting cancer cells to avoid apoptosis [18, 34]. Constant NRF2 activation results in overexpression of a number of NRF2-dependent genes, most of them cytoprotective and antioxidant enzymes. Upregulation of NRF2-mediated gene expression seems to involve genes that may promote cancer cell growth, including growth factors such as

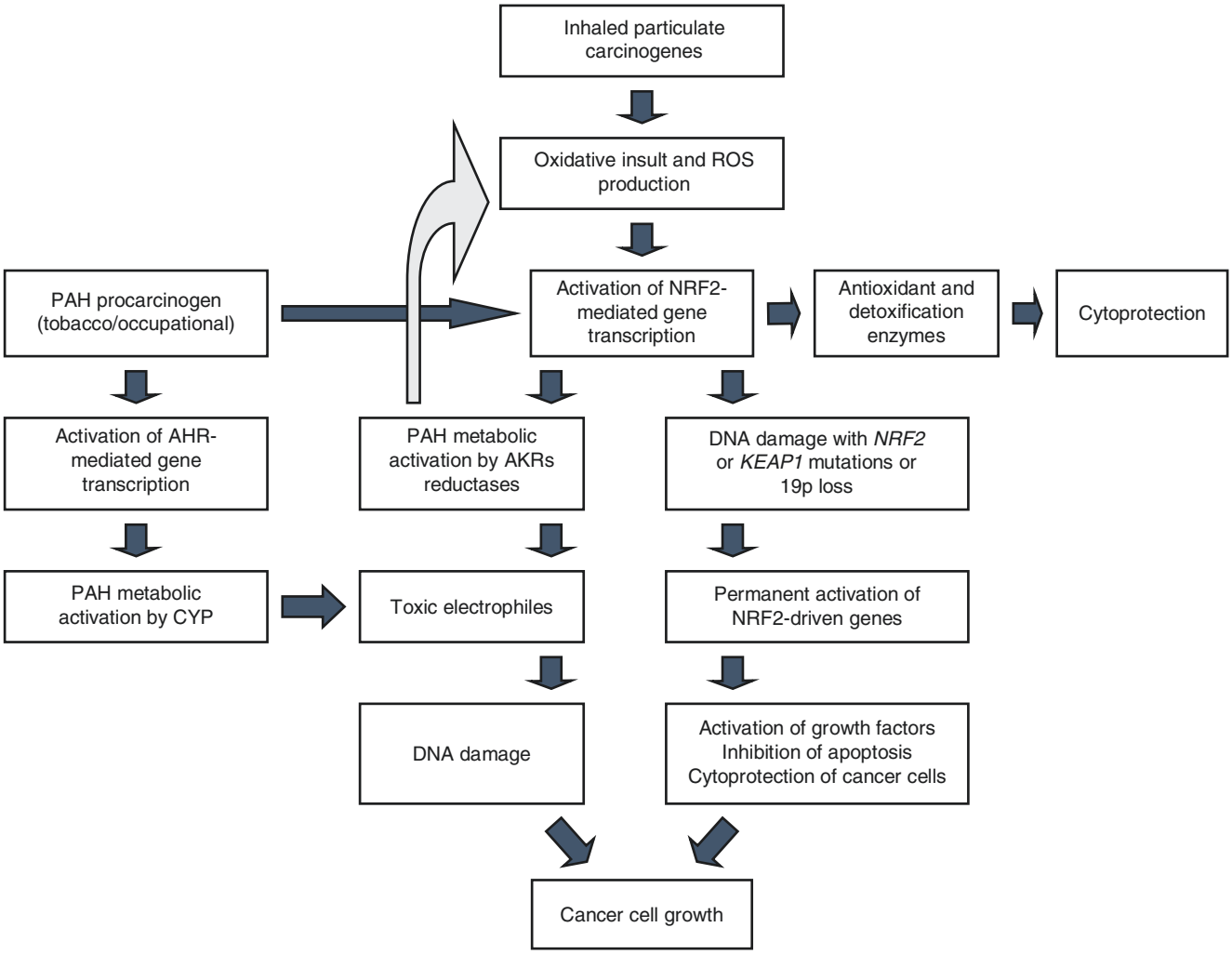

Fig. 13.1 Co-carcinogenesis mechanisms of PAH procarcinogens and oxidative stress damage. *PAH* polycyclic aromatic hydrocarbon, *AKR* aldo-keto reductases

fibroblast growth factor 13, TGF-α, TGF-β1, and -β2, and growth factor receptors [34]. It has been shown that NRF2 activity regulates the sensitivity of death signals and NRF2 overexpression antagonizes apoptosis [35–38]. The antiapoptotic Bcl-2 family proteins are under the regulative control of NFR2, and constant activation of NRF2 leads to overexpression of Bcl-2 and Bcl-xL, decreased apoptosis, and increased survival of cancer cells [37, 38]. Furthermore, one such NRF2-regulated antioxidant enzyme, peroxiredoxin 1 (PRX1), which is commonly upregulated in human cancer, has a dual role as it may provide resistance to oxidative stress in cancer cells by the inhibition of apoptosis signal-regulating kinase 1 (ASK1) activation and subsequent ASK1-induced apoptosis [39].

The enhancement of the oxidative stress and consequent apoptotic pressure by combined exposures to tobacco and particulate carcinogens may lead to DNA damage in critical genes, resulting in uncontrolled expression of NRF2-regulated genes, inhibition of apoptosis, and growth advantage to cancer cells. One of these critical aberrations, the deletion of the 19p chromosomal region, is especially common in asbestos-related lung cancer [32, 40]. The postulated mechanisms of co-carcinogenesis of tobacco carcinogens and oxidative stress are shown in Fig. 13.1.

Biomarkers

Biomarkers of PAH Exposure

The biomarkers of PAH exposure most commonly used are urinary PAH metabolites, in particular 1-hydroxypyrene. 1-hydroxypyrene and other urinary noncarcinogenic and carcinogenic PAH metabolites are thought to reflect total PAH exposure. The level of urinary PAH metabolites is influenced not only by occupational exposure, but also by diet, tobacco

smoking, and environmental air pollution. Typically, in air samples from foundries and petrochemical plants, PAH concentrations are about three orders of magnitude higher than those in environmental exposures. Similarly, urinary 1-hydroxypyrene concentrations reflect the exposure levels well at the group level. PAH-DNA or protein adducts are considered the measure of an effective dose of PAH exposure.

Biomarkers of Oxidative DNA Damage

DNA strand breaks and 8-hydroxyguanine (8-hydroxydeoxyguanosine, 8-oxoGuo, 8-OH-G, 8-OH-dG) formation are the most commonly used tests for oxidative DNA damage caused by exposure to PAH and inhaled particulates in the scientific literature. The oxidized DNA product 8-OH-G is formed in the reaction of guanine with hydroxyl radical [41]. This mutagenic and carcinogenic DNA product is a good biomarker of oxidative stress, and can be determined in urine or circulating white blood cells [41]. 8-OH-G levels in urine are also influenced by gender, age, body mass index, and lifestyle factors, such as tobacco smoking, hard physical labor, and diet [42, 43].

DNA strand breaks can be studied by comet assay (alkaline single-cell gel electrophoresis assay) in cultured cells or in the circulating blood lymphocytes of exposed individuals [44]. Tarantini et al. [45] studied the relative contribution of DNA strand breaks and DNA adducts to the genotoxicity of B[a]P as a pure compound and in complex mixtures collected from an urban peri-industrial site and a metallurgical plant. Treatment of HepG2-cultured human hepatocytes with pure B[a]P or with a fraction of atmospheric particles containing soluble PAH did not induce oxidative DNA damage as measured by DNA strand breaks in comet assay or the formation of 8-oxoGuo, whereas B[a]PDE adducts were observed with even low concentrations. In contrast, samples filtered from industrial and especially those from urban sites induced DNA strand breaks and the formation of 8-oxoGuo, and less BPDE adducts, suggesting that a component other than PAH, possibly particulate matter in the mixture, modulates the genotoxic properties of complex mixtures [45].

The most commonly used biomarkers of internal dose, biologically effective dose, and early effects in relation to occupational exposures to PAH and complex mixtures are listed in Table 13.1.

Metal-Induced Lung Carcinogenesis

Metal-induced carcinogenesis has been covered in detail in several recent reviews cited in this chapter. For more information regarding metal carcinogenesis, readers are referred to these and other literature, and for the basic biological mechanisms of carcinogenesis, Chap. 3 of this book.

Arsenic

Arsenic (As) and its compounds have been identified by IARC as group I human carcinogen, causing cancers of the skin, liver, kidney, bladder, and lung [46]. Globally, arsenite [As(III)] or arsenate [As(V)] is a significant contaminant of drinking water, causing an excess of cancers especially of the skin and bladder. Occupational exposure, via inhalation of As compounds such as arsenic trioxide, arsenic trisulfide, and calcium arsenate, increases lung cancer risk in ore smelters, insecticide manufacture, and sheep dip workers [47].

Oxidative DNA Damage

The inorganic arsenics can be methylated in vivo to form monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) in a process of repeated reductions and oxidative methylations, which enhance excretion from the body. However, methylated arsenicals also have a more adverse effect in human cells than the parent compound. MMA and DMA are also ingredients in weed killer chemicals. Trivalent methylated arsenicals are biologically highly reactive, and can interact with cellular targets such as proteins and DNA [47–50]. As metabolism in cells leads to the generation of a variety of reactive oxygen and nitrogen species, including superoxide, singlet oxygen, hydrogen peroxide, the peroxyl radical, nitric oxide, dimethylarsinic peroxyl radicals, and the dimethylarsinic radical [41, 51]. The exact mechanism for the generation of these reactive species is not clear, but the formation of intermediary arsine species or the oxidation of As(III) to As(V) has been suggested [41, 52]. As(III) and MMA(III) have been shown to cause NRF2 activation via mechanisms involving autophagy and p62, a substrate adaptor protein with a critical role in autophagy [53]. The formation of 8-hydroxyl-2'deoxyguanosine (8-OHdG) DNA adducts is a biomarker of oxidative stress to DNA. Increased levels of 8-OHdG adducts have been detected after exposure to arsenic in cells, animal models, and in arsenic-induced lesions of human skin [51, 52, 54, 55].

Genotoxicity and DNA Repair

Arsenic is not mutagenic in standard assays, but it is genotoxic and induces chromosomal aberrations, sister chromatid exchange, aneuploidy, micronuclei formation, and DNA-protein cross-links [56–59]. As(III) has been demonstrated by alkaline single-cell gel electrophoresis (comet) assay to induce DNA strand breaks in various human and rodent cells [51, 60–62]. As(III)-induced DNA strand breaks are caused by ROS production, and breaks may lead to chromosomal rearrangements. Wang et al. [63] have shown that As(III)-induced DNA strand breaks largely result from excision of oxidative DNA adducts and DNA-protein cross-links during excision repair. As inhibits completion of DNA excision repair via effects on DNA ligase activity perhaps due to

being a phosphate analog and interfering with phosphorylation reactions and phosphate transport [51, 64–67]. Exposure to As has been shown to inhibit critical DNA repair enzymes. Morales et al. [68] demonstrated in a culture assay system that exposure to As trioxide shifted double strand break DNA repair towards error prone non-homologous end joining and inhibited homologous recombination. Exposure to As(III) has also been linked to mismatch repair deficiency and concomitant microsatellite instability in human colorectal cancer cells [69].

Arsenic exposure has been related especially with squamous cell histological lung cancer type [70, 71]. Martinez et al. [72] studied gene copy number alterations in squamous cell lung carcinomas from non-smokers exposed to As in drinking water and observed the most recurrent losses at chromosomal regions 1q21.1, 7p22.3, 9q12, and 19q13.31 and gain at 19q13.33. These findings are in agreement with the ability of As to induce DNA strand breaks and genomic instability. Martinez et al. [73] performed whole-genome sequencing analysis on lung squamous cell carcinoma from a heavily arsenic-exposed non-smoker. They found increased number of copies at 3q26 and overall low number of point mutations, including mutations rarely detected in squamous cell carcinoma of the lung.

Epigenetic Mechanisms

Epigenetic mechanisms, such as methylation, histone modifications and microRNAs are involved in arsenic-induced carcinogenesis. As treatment of rat liver cells and human keratinocytes has resulted in reduced expression and activity of DNA methyltransferases, inducing global DNA hypomethylation [74–76]. As treatment or exposure has also been associated with the silencing of tumor suppressor genes by hypermethylation of their promoter regions, such as *RASSF1A* and *RPSS3* in human bladder cancer [77], *p16(INK4a)* and *RASSF1A* in murine lung cancer [78], *DEPK* in SV-40-immortalized human urothelial cells and in human urothelial (bladder) carcinomas from the arsenic-contaminated area [79, 80], *TP53* in human lung adenocarcinoma A549 cells [81], and *TP53* and *P16(INK4A)* in whole blood DNA of people exposed to arsenic in drinking water [82]. Both the global hypomethylation and hypermethylation of promoter regions of tumor suppressor genes are common alterations in malignant tumors. It has also been shown that As(III) changes global histone H3 methylation levels in human lung adenocarcinoma A549 cells [76, 83] and in blood mononuclear cells of individuals exposed to arsenic in drinking water [76, 83, 84].

MicroRNAs are a family of small non-coding RNA molecules that negatively regulate protein-coding gene expression. Aberrant expression of non-coding RNAs and the consequent disruption of signaling pathways have been implicated in As-induced carcinogenesis [85, 86]. As exposure activates several signal transduction pathways which enhance cell proliferation or reduce antiproliferative signaling, inhibit differentiation, and override the cell cycle checkpoints that control cell division and apoptosis [86]. Downregulation of microRNAs of miR-200 family and upregulation of miR-21 (oncomiR-21) are involved in arsenite-induced malignant transformation of human bronchial epithelial cells [87, 88].

Arsenic as a Co-carcinogen

Arsenic is a powerful co-carcinogen and is able to enhance the carcinogenicity of other agents, such as ultraviolet and ionizing radiation, benzo[a]pyrene, *N*-methyl-*N*-nitrosourea, diepoxybutane, and methylmethane sulfonate in cell and animal models [65, 66, 89–95]. There is epidemiological evidence of the synergistic effect of ingested As and tobacco smoking on lung cancer risk [96, 97]. A Taiwanese study demonstrated the synergy for the squamous and small cell but not for the adenocarcinoma of the lung [98]. The same group demonstrated that As increased the metabolism of a tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), via activation of Cyp2a in mouse liver, and the metabolism of another tobacco carcinogen, benzo[a]pyrene, by enhancement of CYP1A1 expression and activity via the AH receptor with a mechanism involving oxidative stress, in a human adenocarcinoma cell line [101, 102]. CYP enzymes catalyze the initial step (Phase I) in the metabolism of nitrosamine and PAH procarcinogens, including benzo[a]pyrene, which is necessary for the subsequent reactions leading to the formation of DNA-reactive metabolites, as well as detoxification (Fig. 13.1).

Beryllium

Beryllium (Be) and beryllium-containing compounds are classified as human carcinogens or likely human carcinogens, causing lung cancer [46, 103]. Much of the human epidemiological data demonstrating increased lung cancer risk are associated with very high exposures which took place before the 1950s in plants involved in the extraction of beryllium hydroxide from beryl ore, ore refining, and beryllium processing including the production of beryllium oxide, pure beryllium metal, and beryllium copper alloy, and the machining of beryllium-containing materials [103].

There is no extensive research data concerning the mechanisms of beryllium-related carcinogenesis. Gordon and Bowser have reviewed the studies on the genotoxicity and carcinogenicity of beryllium [104]. The different chemical forms have had differing effects on mutagenicity and carcinogenicity and there are no data concerning the beryllium forms relevant to human exposures, i.e., respirable size particles of beryllium metal, alloys, or ceramics [103, 104].

Mammalian test systems have shown evidence of beryllium-induced mutations, chromosomal aberrations, and cell transformation, whereas bacterial tests have been negative [104].

Epigenetic alterations have been detected in beryllium metal-induced rat lung tumors. Belinsky et al. observed hypermethylation of the promoter, and loss of transcription in the *p16(INK4a)* tumor suppressor gene in 80% of beryllium-induced rat lung tumors [105].

Cadmium

Cadmium (Cd) is classified as a human lung carcinogen by the International Agency for Research on Cancer [46]. Exposure to Cd is common because the metal is widely used in industry, for example in electroplating, paints and pigments, welding, and in Nickel-Cd batteries. Significant amounts of Cd are also released into the environment by human activities [106]. An emerging source of exposure is cadmium-based quantum dots, which are light-emitting nanoparticles used as fluorescent labels in bioimaging and biodiagnostic applications [107, 108]. Moreover, Cd is present in the earth's crust, and is selectively taken up by certain edible plants and by for example the tobacco plant, making tobacco smoke a significant source of Cd for smokers. The amount of Cd stored in organs depends on their content of a Cd-binding protein, metallothionein. The half-life of Cd in humans is 15–20 years; in lung tissue, Cd is cleared with a half-life of 9 years after quitting smoking [106, 109].

Oxidative DNA Damage

Several mechanisms contribute to the carcinogenicity of Cd [106, 110]. Cd is a weak genotoxic agent and its genotoxicity, i.e., chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA-protein cross-links, is partially mediated by oxygen radical damage [106, 111–113]. Cd is able to induce the generation of ROS in vitro and in vivo, including superoxide anion, hydrogen peroxide, hydroxyl radical, and lipid radicals, in spite of not functioning as a catalyst in the Fenton reaction [110]. It has been proposed that Cd can replace iron and copper in cytoplasmic and membrane proteins, thus increasing the amount of free or chelated copper and iron, which in turn may induce oxidative stress via Fenton reactions [41, 114]. Following exposure to Cd, several transcription factors and pathways are activated that are responsive to oxidative stress, including transcription factors AP-1, NF-κB, and NRF2, and mitogen-activated protein kinases (MAPKs) signal transduction pathways [110]. MAPKs play an important role in programmed cell death (apoptosis) for the elimination of cells with oxidative DNA damage.

Recent research reports have highlighted the significance of NRF2/p62 pathway in metal-induced carcinogenesis. The p62 is ubiquitin-binding scaffolding protein with a critical role in the cellular processes of autophagy and oxidative stress signaling [116]. It has been shown that Cd induces malignant transformation of human bronchial epithelial cells via ROS production, and that Cd-transformed cells exhibit dysfunction of autophagy resulting in p62 overexpression and accumulation [117, 118]. The p62 interacts with the NFR2-binding site of KEAP1, the repressor protein of NRF2, leading to constitutive NRF2 activation, and consequently, high expression of antioxidant and antiapoptotic proteins, apoptosis resistance, and increased cancer cell survival and proliferation [117].

DNA Repair

The potential of Cd to inhibit the repair of oxidative DNA damage has been demonstrated in several in vitro and in vivo studies, and it is considered a major mechanism of Cd-induced carcinogenesis [106, 119, 120]. The repair mechanisms reported to be inhibited by Cd include nucleotide excision repair, non-homologous end joining, base excision repair, and mismatch repair (Morales et al. [68] and references therein). Inhibition of DNA damage repair by Cd is thought to be attributable to its effects on enzymes involved in oxidative damage repair, as Cd can be substituted for zinc in zinc-finger proteins, resulting in the enzyme's defective repair capacity [106, 121]. Morales et al. [68] demonstrated in a cell culture assay system that low doses of nickel and Cd promote mutagenic non-allelic recombination as a major repair pathway of DNA double strand breaks. Cd has also been shown to increase microsatellite instability concomitantly with ROS production and decreased levels of mismatch repair proteins [69].

Epigenetic Mechanisms

The role of epigenetic mechanisms in Cd carcinogenesis is uncertain [74]. In human prostate cells and in another study using rat liver cells, Cd initially induced global DNA hypomethylation followed by hypermethylation after prolonged exposure [122, 123]. In human prostate cells, promoter hypermethylation and reduced expression of *RASSF1A* and *p16* tumor suppressor genes were observed [122]. It is hypothesized that global DNA hypomethylation is associated with Cd-induced cell proliferation [74, 124]. The possible effect of Cd on histone tail posttranslational modifications is not known [74].

Chromium

Chromium VI [hexavalent chromium, Cr(VI)] compounds have been identified as human lung carcinogens [46]. Cr(VI) is widely used in a variety of industries, for example in paints, metal finishes, stainless steel manufacturing, alloys,

welding, and in wood treatment. In contrast to other oxidation states of Cr, Cr(VI) is easily transported into cells by an anionic transport system, and subsequently reduced to lower oxidation states by a number of reducing agents, such as glutathione, NADPH-dependent glutathione reductase, ascorbate, cysteine, lipoic acid, hydrogen peroxide, fructose, and ribose [125, 126]. It is thought that Cr(III) is unable to cross cell membranes, but recently it has been suggested that certain Cr(V) and Cr(III) forms generated by reduction in the extracellular space have high permeability through cell membranes [41, 127, 128]. Insoluble Cr compounds can enter cells via phagocytosis. Particulate or water-insoluble Cr(VI) compounds are more potent than soluble species in causing DNA damage, possibly because of the fast clearance of soluble Cr(VI), whereas poorly soluble particulates may form a persistent source of carcinogenic Cr species in the lung [129, 130].

Oxidative DNA Damage and Genotoxicity

Intracellular reduction of Cr(VI) is the main source of reactive intermediates and the extensive formation of Cr-DNA adducts and subsequent DNA damage [41, 86, 126]. Cr(V), when formed, can have a Fenton-like reaction with hydrogen peroxide, generating hydroxyl radical. Associated other reactions can produce thiyl and superoxide radicals [41, 126]. In addition to free radical induced DNA damage, the formation of Cr-DNA adducts, above others Cr(III)-mediated DNA cross-links of glutathione, cysteine, histidine, and ascorbate, is responsible for the mutagenicity and genotoxicity of Cr(VI) [41, 131]. Other Cr-induced structural genetic lesions include DNA strand breaks, DNA-protein cross-links, oxidized bases, abasic sites, and DNA-inter- and intra-strand cross-links [126, 132]. Wakeman et al. [133, 134] have shown that exposure to the unstable intermediates Cr(V) and Cr(IV), generated during the reduction of Cr(VI) to Cr(III), can induce highly genotoxic DNA double strand breaks. While Cr(VI) is not able to directly interact with DNA and exposure to Cr(V) resulted in the initiation of cell cycle checkpoints, exposure to Cr(IV) failed to activate optimal DNA damage response and caused a high frequency of mutations, supporting the role of Cr(IV) as the ultimate mutagenic species [134]. The group also found that a mismatch repair protein MLH1 is required for the activation of the G2/M cell cycle checkpoint in response to Cr exposure.

DNA Repair

The DNA damage caused by Cr can lead to dysfunctional DNA replication and transcription and promote genomic instability by dysregulated repair mechanisms, especially by loss of mismatch repair. Microsatellite instability (MSI) reflects the loss of functional mismatch repair mechanism. A Japanese group has compared the presence of replication error phenotype between lung cancers in chromate-exposed and non-exposed individuals. They observed significantly more frequent MSI and repression of DNA mismatch repair proteins MLH1 and MLH2 in the lung cancers of chromate-exposed workers [135, 136]. These findings are contradicted by the lung cell experiments by Rodrigues et al. [137], who observed aneuploid phenotype but did not find MSI or reduced expression of mismatch repair proteins in human bronchial epithelial cells malignantly transformed by hexavalent Cr. These differences suggest that replication error phenotype may not be the initial event leading to cancer development in chromate-exposed workers.

In earlier studies on chromate-exposed lung cancer patients, mutations of *RAS* oncogenes and *TP53* tumor suppressor gene were infrequent [138, 139]. However, *TP53* mutations were unusual changes of AT base pairs and double missense mutations [139].

Epigenetic Mechanisms

Chromates have induced gene expression changes by epigenetic mechanisms in tumor suppressors and other critical genes both in experimental settings and in vivo. Interesting data have been published concerning mechanisms contributing to the co-carcinogenesis of hexavalent Cr and a model polycyclic aromatic hydrocarbon procarcinogen, benzo[a]pyrene. In mouse hepatoma cells, treatment with potassium chromate represses the expression of the benzo[a]pyrene-metabolizing Cyp1a1 enzyme, blocking the detoxification pathway, and consequently enhances the formation of benzo[a]pyrene-diol-epoxide-DNA adducts [115]. It was shown that Cr cross-links histone deacetylase 1-methyltransferase complexes to the Cyp1a1 promoter and inhibits gene transcription. The same research group previously demonstrated approximately 50 other benzo[a]pyrene-inducible genes that were repressed by Cr in a similar manner, including receptor-associated kinases, transcription factors, and genes associated with cell cycle regulation, differentiation, and apoptosis [140]. In human lung adenocarcinoma cell line, potassium chromate induced global changes in various histone tail modifications, including an increase in H3K9 dimethylation in the promoter of the DNA mismatch repair gene, *MLH1*, and a decrease of its expression [141]. Furthermore, hypermethylation of the promoter regions of several tumor suppressor genes, particularly *MLH1*, *APC*, and *P16* genes, has been reported in lung carcinomas of patients with over 15 years' occupational exposure to chromates [142, 143].

Cr has also been shown to exert its cell transformation capacity via induction of a stress response protein NUPR1 (nuclear protein 1 or p8). NUPR1 regulates key cellular functions, such as cell cycle, apoptosis, autophagy, chromatin accessibility, and transcription, via interactions with molecular partners [144]. Exposure to Cr(VI) induces NUPR1 overexpression, which decreases the level of histone

H4K16 acetylation leading to the transcriptional downregulation at several genomic loci, thereby contributing malignant transformation [145].

Recent literature has highlighted the role of microRNAs in Cr(VI)-induced malignant transformation. He et al. [146] found that miR-143 was downregulated in Cr(VI)-transformed human bronchial epithelial cells. Pratheeshkumar et al. [147] showed that exposure to Cr(VI) increased (onco) miR-21 levels in human bronchial epithelial cells, resulting in inhibition of the tumor suppressor programmed cell death 4 (PDCD4), and furthermore, knockdown of miR-21 significantly reduced the Cr(VI)-induced cell transformation.

Nickel

All nickel [Ni(II)] compounds are classified into group I human carcinogens, which can cause nasal and lung cancer, and metallic Ni as possibly carcinogenic to humans (Group 2B) [46]. Ni is an abundant element in the earth's crust. It is used in the metallurgical industry in the production of stainless steel and alloys, in electroplating, stainless steel welding, Ni-Cd batteries, and in the production of nanoparticles [148]. Ni pollution in the environment originates from the combustion of fossil fuels in vehicles and power plants, industrial sources, waste incinerators, disposal of Ni compounds, and volcanic eruptions. Ni also deposits in the soil and plants, which increases exposure via food, drinking water, and tobacco smoking.

Inhalation is the main route of exposure for workers exposed to carcinogenic Ni compounds in industry. While both soluble and poorly soluble Ni compounds are considered carcinogenic, water-insoluble compounds, which enter cells via phagocytosis, are readily dissolved in cellular lysosomes and generate high intracellular levels of Ni^{2+} cations and consequently exhibit higher cytotoxicity and genotoxicity [149]. Potential carcinogens are insoluble dusts of nickel subsulfides and nickel oxides, the vapor of nickel carbonyl, and the soluble aerosols of nickel sulfate, nitrate, or chloride [150].

Genotoxicity

Although Ni compounds are not mutagenic in traditional mutation tests, they can induce malignant transformation in human and rodent cells [149, 151–155]. Soluble and insoluble Ni compounds induce genetic abnormalities, preferentially in heterochromatin. Genetic aberrations, such as DNA strand breaks, DNA-protein cross-links, deletion/insertion and single gene mutations, sister chromatid exchanges, micronuclei, and microsatellite mutations have been observed in mammalian or human cells in vitro [156].

Compared with Cd and Cr, Ni is a weak inducer of oxidative stress [157, 158]. However, the reactivity of Ni with oxygen derivatives can be modulated by chelation with certain histidine- and cysteine-containing ligands, and free radicals may arise from the reaction of Ni(II)-thiol complexes and molecular oxygen, or lipid hydroperoxides [158]. G → T transversion mutations, typical of oxidative DNA damage, have been detected in codon 12 of K-ras oncogene in rat renal sarcomas induced with nickel subsulfide and iron [159]. Several Ni compounds have been shown to increase oxidative DNA damage and the formation of 8-hydroxydeoxyguanosine (8-OH-dG) adducts in cultured cells and in rat lungs after intratracheal instillation of Ni compounds [160]. Furthermore, high levels of 8-OH-dG adducts and the DNA repair marker 8-hydroxyguanine DNA glycosidase 1 have been detected in blood cells of Ni-smelting workers [161]. Son et al. have shown that the ROS-inducible transcription factor NRF2 is constitutively highly expressed in Ni-transformed human bronchial epithelial cells [162]. NRF2 overexpression increases autophagy via STAT3 signaling, and upregulates the expression of antioxidant and antiapoptotic proteins, contributing to apoptosis resistance and tumorigenesis [162].

Epigenetic Mechanisms

Epigenetic mechanisms are considered more important than genetic changes in nickel-induced carcinogenesis (see also Chap. 3). Nickel binds to heterochromatin rather than euchromatin, where it alters the heterochromatin structure, causing chromatin condensation, inhibition of histone H4 acetylation, and de novo DNA methylation [74, 149, 163, 164]. Ni^{2+} is able to displace Mg^{2+} in the phosphate backbone of DNA and increase the level of chromatin condensation and subsequent DNA methylation and heterochromatinization [165]. Histone acetylation is necessary for transcriptional activation. Ni restricts the acetylation of histone H4 by binding with its N-terminal histidine-18 and by influencing histone acetyltransferase (HAT) activity [166–168]. Ni also increased histone H3K9 dimethylation ($H3K9me^2$) in a transgene when the transgene was integrated near the heterochromatin region [169]. Jose et al. [170] showed that Ni can disrupt $H3K9me^2$ domain structures genome-wide, resulting in spreading of $H3K9me^2$ into the active genomic regions and gene silencing. The group suggested a mechanism involving the inhibition of the insulator protein CCCTC-binding factor at the $H3K9me^2$ domain boundaries. Chen et al. [99, 100] demonstrated that Ni inhibits the activation of dioxygenase enzymes, such as histone demethylase MJD1A and DNA repair enzyme ABH2, by replacing the non-heme iron at their catalytic center. The loss of histone acetylation and de novo DNA methylation silence genes, and the silencing of critical genes, such as tumor suppressor genes, contributes to carcinogenesis.

The promoter of tumor suppressor gene *p16* has been constantly hypermethylated in the nickel sulfide-induced

malignant fibrous histiocytomas of wild-type mice and mice heterozygous for the tumor suppressor *p53* gene [171]. Also, methylation has been observed in the enhancer regions of *RAR-β2*, *RASSF1A*, and *CDKN2A* genes of rat muscle tumors induced by nickel subsulfide [172]. Histone modifications have been studied in peripheral blood mononuclear cells of Ni refinery workers, steel workers, and Ni-smelting workers. In these worker groups, changes in histone H3 methylation and acetylation were observed as compared to non-exposed referents, and some of the changes correlated with the length of the employment [173–175].

Hypoxic Signaling

Activation of hypoxic signaling is another main alteration with significance in Ni-induced carcinogenesis. Gene expression profiling with Affymetrix chips on wild-type or the hypoxia-inducible factor-1 (HIF-1) knockout mouse embryo cells found that after $NiCl_2$ treatment, 114 genes were upregulated and 66 genes downregulated in a manner characteristic of the activation of the hypoxic signaling pathway [176]. The HIF-1 transcription factor is a dimer consisting of two subunits, HIF-1α and HIF-1β (ARNT), which is formed in response to low oxygen tension in cells, and together with transcriptional co-activators, regulates the transactivation of HIF-dependent genes. HIF-1α acts as an oxygen sensor, which in the presence of hypoxia or Ni, avoids ubiquitylation and proteosomal degradation and accumulates in cells [86]. Hypoxic signaling is thought to be one of the pathways that Ni exposure can induce by disrupting cellular iron homeostasis [177, 178]. In hypoxic cancer and stromal cells, HIF-1 transactivates growth and survival factors, such as VEGF, FGF, PAI-I, adrenomedullin, and NOS, which induce endothelial cell proliferation, migration, invasion, and angiogenesis [149].

DNA Repair

Nucleotide and base excision repair pathways are impaired by Ni compounds, at least partially by the damage of zinc fingers in DNA repair proteins [179]. Morales et al. [68] studied in a culture assay system how Ni exposure modifies DNA double strand break repair outcomes and found that $NiCl_2$ favors repair through non-allelic recombination events with a significant increase of non-templated sequence insertions at the repair site. Scanlon et al. [180] demonstrated that Ni exposure downregulates the DNA repair proteins which are involved in homology-dependent DNA double strand break repair (HDR) and mismatch repair (MMR) in human bronchial epithelial cells and in lung adenocarcinoma cells in a dose-dependent manner. Interestingly, these functional changes in DNA repair were similar to those induced by hypoxic stress.

Ni compounds induce carcinogenesis by a number of different mechanisms, including genetic and epigenetic changes, affecting signal transduction pathways, especially hypoxic signaling, and inhibiting DNA repair. There is evidence that Ni interferes with cellular metabolism by disrupting iron homeostasis and inhibiting the function of iron-dependent enzymes.

Mechanisms of Ionizing Radiation-Induced Carcinogenesis

Ionizing radiation-induced DNA damage is described in more detail in Chap. 3 and illustrated in Fig. 3.1. Exposure via inhalation to uranium-containing particles and radon decay products, including high linear energy transfer (LET) alpha-particles, through the mining and processing of ore for nuclear power and weapons is associated with increased lung cancer risk [181]. Uranium is a radioactive heavy metal, the radioactivity of which is attributable to the ^{222}Rn and ^{220}Rn isotopes and their decay products. Studies among miners have been complicated by complex exposures to particulate and non-particulate matter in mines, including arsenic, silica, and diesel exhaust [182, 183].

Ionizing radiation (IR) produces reactive oxygen and nitrogen species that are responsible for oxidative stress and inflammatory response. The inflammatory reaction and oxidative damage is dependent on the dose of IR. Large deletions resulting in partial or complete deletion of entire genes, and loss of heterozygosity in the neighboring chromosomal regions are the predominant event induced by alpha irradiation in vitro [182, 184]. High-LET alpha-emitters including radon, plutonium, and Thorotrast, induce double strand breaks and clustered lesions, which are more difficult to repair than single strand breaks and depurinated, oxidized or deaminated bases, produced by low-LET X-rays and gamma-rays [185–189]. High-LET alpha-emitters also induce genomic instability through the inactivation of DNA mismatch repair [190, 191]. Most DNA damage produced by IR is repaired by base excision repair, and nucleotide excision repair, double strand break repair, and mismatch repair have lesser roles [192]. Erroneous rejoining of double strand breaks can result in genomic instability.

In normal cells, IR induces apoptosis or cellular senescence through increased expression of tumor suppressor genes *P16(INK4A)* and *TP53* via the DNA damage response. An early study has reported a predominance of the *TP53* codon 249 AGGarg →ATGmet mutation in lung cancer of uranium miners, whereas subsequent studies have failed to show any mutational hotspots related to radon exposure [193, 194]. There is evidence that epigenetic changes are related to exposure to IR and its early biological effects. The cumulative exposure to radon gas in Chinese uranium miners correlated positively with promoter hypermethylation of the *P16(INK4A)* tumor suppressor and *O^6-methylguanine-DNA*

methyltransferase (MGMT) DNA repair genes in sputum [195]. In another cohort of New Mexico uranium miners, exposure to radon gas did not increase the aberrant methylation of these genes in sputum, as compared to exposure to tobacco smoke alone [196]. Belinsky et al. [197] have shown a higher prevalence of *P16(INK4A)* promoter methylation in the lung adenocarcinomas of workers exposed to ^{239}plutonium than that among non-exposed controls.

Conclusion

Many carcinogenic chemicals, including polycyclic aromatic hydrocarbons, present in combustion products and tobacco smoke, enter cells as procarcinogens and require metabolic activation by cytochrome P450 (CYP) enzymes to exert their deleterious effects, including binding to DNA and formation of DNA adducts which, if not repaired, may lead to mutations in critical genes and cancer initiation. The induction of oxygen radical damage is considered the main mechanism of particle and metal carcinogenesis. In workplace air many carcinogens exist as complex mixtures, in which chemical compounds are bound to metal and mineral particles of respirable size. In lung cells, the components of complex mixtures induce oxidative stress as well as activation of chemical procarcinogens via intermingled pathways that may potentiate the DNA damage caused by either particle or chemical carcinogen alone. Carcinogenic metals are thought to induce oxidative stress-mediated DNA damage. Recent studies have shown that carcinogenic metals may replace metal ions, such as iron and zinc, in critical enzymes involved in DNA repair, histone methylation, and hypoxic signaling, for example. Epigenetic carcinogenic mechanisms have recently been found to play a larger role than previously thought, in environmental carcinogenesis.

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