PART 1.

CONCORDANCE BETWEEN CANCER IN HUMANS AND IN EXPERIMENTAL ANIMALS

CHAPTER 3.

Arsenic and metals

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Arsenic and arsenic compounds together with various metals, specifically including beryllium and beryllium compounds, cadmium and cadmium compounds, chromium(VI) compounds, and nickel and nickel compounds, were re-evaluated in *IARC Monographs* Volume 100C (IARC, 2012) as *carcinogenic to humans* (Group 1). The most recent earlier evaluations appeared in Volume 84 (IARC, 2004) for arsenic, Volume 58 (IARC, 1993) for beryllium and cadmium, and Volume 49 (IARC, 1990) for chromium and nickel.

Arsenic and arsenic compounds

Carcinogenicity

Early on, exposure to inorganic arsenic via drinking-water or oral use of arsenic-based drugs was considered carcinogenic to the skin in humans, and exposure to inorganic arsenic via inhalation in occupational settings was evaluated as carcinogenic to the lung in humans (IARC, 1973). Arsenic was most recently assessed as a contaminant of drinking-water (IARC, 2004). The most prevalent source of human exposure to arsenic is now drinking-water, where it is found primarily as the inorganic forms of arsenite and arsenate. Inorganic arsenic can be metabolized by most mammals to form trivalent and pentavalent methylated metabolites through specific methyltransferases, with *S*-adenosylmethionine as the methyl donor (IARC, 2004, 2012). Questions remain about the relative contribution of the inorganic and the methylated arsenic species to the overall carcinogenic potential of exposure to arsenic. Arsenic and arsenic compounds in drinking-water are human carcinogens; there is *sufficient evidence* in humans for cancer of the lung, urinary bladder, and skin, as well as *limited evidence* for cancer of the kidney, liver, and prostate (IARC, 2004, 2012).

In rodents, transplacental arsenic exposure via maternal consumption of sodium arsenite in drinking-water during gestation induced bronchiolo-alveolar carcinoma in the adult offspring in C3H/HeNCr mice (two studies) and CD1 mice (IARC, 2012). In addition, in a study of CD1 mice with "whole-life" exposure to multiple levels of sodium arsenite in drinking-water from 2 weeks before breeding (male and female mice), during gestation and lactation (female mice), and after weaning until age 2 years (offspring, both sexes), bronchiolo-alveolar carcinoma occurred in a dose-related fashion in both male and female offspring (Tokar et al., 2011). In CD1 mice, in utero exposure via maternal consumption of sodium arsenite in drinking-water during gestation with or without subsequent dimethylarsinic acid (DMA(V)) in drinking-water of the offspring throughout adulthood induced bronchiolo-alveolar carcinoma in animals that received prenatal arsenite alone, DMA(V) alone, or the combination of prenatal arsenite and DMA(V) (Tokar et al., 2012a). In CD1 mice, in utero exposure to arsenic via maternal consumption of monomethylarsinous acid (MMA(III)) in drinking-water produced bronchiolo-alveolar

carcinoma in male offspring as adults, but not in a dose-related fashion (Tokar et al., 2012b). Multiple intratracheal instillations of inorganic arsenic produced lung tumours in hamsters (three studies) (IARC, 2012). In adult strain A/J mice, oral sodium arsenate increased the size and multiplicity of lung tumours (male mice), and oral DMA(V) increased the incidence and multiplicity of lung tumours (IARC, 2012). Oral exposure to DMA(V) increased the incidence of lung tumours in *Ogg*−/− mice, which cannot repair certain types of oxidative DNA damage, but not in *Ogg*+/+ mice (IARC, 2012).

Multiple studies in humans have found oral arsenic exposure to be carcinogenic to the urinary bladder, typically producing transitional cell carcinoma (IARC, 2004, 2012). Most oral exposure in humans would involve inorganic arsenic as the primary form. Multiple studies in rodents show that chronic oral exposure to DMA(V) causes transitional cell carcinoma of the urinary bladder in adult rats, but not in mice (IARC, 2012). DMA(V) exposure can be from the drinking-water or the feed. Exposure to inorganic arsenic has not been shown to be carcinogenic to the urinary bladder in rodents; the reasons for this are not clear.

Gallium arsenide is considered *carcinogenic to humans*, based largely on one robust study in rodents together with ancillary evidence (IARC, 2006). Chronic inhalation of gallium arsenide induced lung bronchiolo-alveolar adenoma or carcinoma in a dose-related fashion in female F344 rats, but not in male rats or male or female B6C3F1 mice (IARC, 2006, 2012). Male rats exposed to gallium arsenide did show dose-related increases in the number of pre-neoplastic lesions (atypical hyperplasia) of the lung epithelium. The role of the separate moieties of the inhaled compound (i.e. gallium and arsenic) in the carcinogenic response could not be defined by this one study in rodents, and it was concluded that either moiety alone or some combination of both could be active (IARC, 2006).

There is *limited evidence* that the liver is a target site for the carcinogenic effects of arsenic and arsenic compounds in humans (IARC, 2012). In rodents, multiple studies showed that in utero exposure to arsenic via maternal consumption of sodium arsenite in drinking-water during gestation induced hepatocellular carcinoma in the adult offspring of C3H/HeNCr mice (two studies) and CD1 mice (IARC, 2012). In addition, in a study of CD1 mice with "whole-life" exposure to multiple levels of sodium arsenite in drinking-water (see above), hepatocellular carcinoma occurred in a dose-related fashion in both male and female offspring (Tokar et al., 2011). In CD1 mice, in utero exposure via maternal consumption of sodium arsenite in drinking-water during gestation with or without subsequent DMA(V) in the drinking-water of the offspring throughout adulthood induced hepatocellular carcinoma in animals that received prenatal arsenite alone or the combination of prenatal arsenite and DMA(V). The combined treatment produced hepatocellular carcinoma at a significantly higher rate than prenatal arsenite alone or DMA(V) alone (Tokar et al., 2012a). In CD1 mice, in utero exposure to arsenic via maternal consumption of MMA(III) in drinking-water produced hepatocellular carcinoma in male offspring as adults (Tokar et al., 2012b).

In multiple studies in rodents, inorganic arsenic or DMA(V) given in drinking-water or by the transplacental route had initiating, promoting, or co-carcinogenic activity in the skin, kidney, and urinary bladder with other, non-arsenic-based compounds (IARC, 2004, 2012). Multiple studies in humans have found oral arsenic exposure to be carcinogenic to the skin and urinary bladder, and there is *limited evidence* that the kidney is a target site in humans (IARC, 2004, 2012). It is difficult to assess the relevance to humans of rodent studies that use multiple agents, one of which is an arsenic compound of concern.

Overall, the target sites for which there is *sufficient evidence* in humans for the carcinogenicity of arsenic and arsenic compounds include the urinary bladder and the lung, and there are multiple concordant rodent studies for these two sites (IARC, 2012). The skin is also a target site in humans for inorganic arsenic and arsenic compounds, but in rodents there is *insufficient evidence* that inorganic arsenic or arsenic compounds acting alone can cause cancer of the skin (IARC, 2012). There is *limited evidence* that the liver is a target site for the carcinogenic effects of arsenic and arsenic compounds in humans, and *sufficient evidence* that the liver is a target site in rodents (IARC, 2012). There is *limited evidence* that the kidney is a target site in humans (IARC, 2012), and one recent study in mice provided evidence that cancer of the kidney can be induced by a combination of inorganic arsenic (prenatal) and DMA(V) in adulthood (Tokar et al., 2012a). There is *limited evidence* that the prostate is a target site in humans, and there are no studies in rodents showing increased incidence of prostate cancer after

exposure to inorganic arsenic or arsenic compounds (IARC, 2012). Inorganic arsenic can cause lung cancer in humans after inhalation or ingestion, but there are no studies showing development of lung cancer in rodents after inhalation exposure (IARC, 1973, 2012). In fact, an adequate inhalation study in rodents with inorganic arsenic has never been performed, presumably because the agent had already been declared a human carcinogen and rodent research resources were directed elsewhere.

Mechanisms of carcinogenesis

Although a unifying mechanistic hypothesis for arsenic-induced carcinogenesis may seem reasonable, it is important to emphasize that given the multitude of toxic events at the subcellular level seen with inorganic arsenic and arsenic compounds (e.g. oxidative stress, altered DNA repair, altered DNA methylation, gene amplification, and altered growth factors), it is likely that multiple mechanisms are operative in arsenic-induced carcinogenesis (Kitchin and Conolly, 2010; Tokar et al., 2010; Hartwig, 2013). These multiple mechanisms are probably linked, at least in part, to the qualities of specific target tissue (e.g. high oxygen tension in the lung might favour oxidative stress, in contrast with the situation in the bladder) (Kitchin and Conolly, 2010). The target tissue-specific toxicokinetics of arsenic are likely to be key and may dictate that multiple toxic events combine into a target-specific carcinogenic mechanism (Kitchin and Conolly, 2010).

In humans, arsenic causes transitional cell carcinoma of the urinary bladder (IARC, 2012), which is the same tumour type induced in rats by chronic oral exposure to DMA(V) (IARC, 2012). Some researchers believe that the rat is a poor model for studying arsenic toxicology in humans, because the toxicokinetics of arsenic are dramatically different as a result of sequestration of arsenic in the blood of rats (Carter et al., 2003; Aposhian et al., 2004). However, for DMA(V) and cancer of the urinary bladder, there is clear site concordance between humans and rats. For bladder tumours induced by DMA(V) in the rat, the mechanism may involve sustained cytotoxicity, possibly from oxidative stress (Kitchin and Conolly, 2010), followed by cell proliferation and genomic instability. Specific methylated forms of arsenic may be involved in the sustained cytotoxicity (Cohen et al., 2007).

Inorganic arsenic and methylated arsenic metabolites generally show weak activity as mutagens. Low-dose exposure to inorganic arsenic can increase the number of mutations resulting from genomic instability, perhaps through production of reactive oxygen species, and cells that methylate inorganic arsenic show much more oxidative DNA damage than cells that poorly methylate the metalloid during in vitro malignant transformation (Kojima et al., 2009). MMA(III) may be one of the most deleterious arsenic methylation products, although the number of tumour end-point studies is very limited (only one study). The main cascade of mechanisms leading to carcinogenesis for inorganic arsenic and arsenic compounds after exposure to low concentrations could include the rapid induction of oxidative DNA damage and inhibition of DNA repair, followed by changes in DNA methylation patterns, aneuploidy, and gene amplification. Gene amplification, altered DNA methylation (epigenetic effects), or aneuploidy may cause alterations in gene expression that lead to genomic instability and cellular transformation. The metabolism of inorganic arsenic by methylation may contribute to its epigenetic effects, because the arsenic methylation pathway overlaps with DNA methylation by consumption of *S*-adenosylmethionine as the common methyl donor (Brocato and Costa, 2013). However, it is noteworthy that inorganic arsenic can cause malignant transformation in cells that do not methylate the metalloid, indicating that neither methylation nor a methylated metabolite are required for a cell to acquire a malignant phenotype after exposure to inorganic arsenic (Kojima et al., 2009). Thus, cell-specific, complex, multifaceted mechanisms are likely to be operative with arsenic (Kitchin and Conolly, 2010; Tokar et al., 2010).

Another important issue with mechanistic implications is the strong evidence that cancer can develop long after elevated arsenic exposure ends. For instance, a recent study on a human population in Chile measured rates of cancer of the bladder and lung in individuals who were highly exposed to inorganic arsenic in drinking-water during 1958–1970 but drank low-arsenic water thereafter. These subjects still showed very high risks of cancer even 40 years after the high exposures ended (Steinmaus et al., 2013). Similarly, the mouse transplacental model demonstrated that brief exposure to inorganic arsenic may result in tumours in adulthood (IARC, 2012). Given the time lag between arsenic exposure and development of cancer, the operative mechanisms would appear not to require concurrent high tissue levels of arsenic.

In discerning mechanisms of arsenic-induced carcinogenesis by use of in vitro model systems, the consideration that arsenic adversely alters many cellular physiological functions is critical; studies have frequently been carried out with levels of arsenic that would be highly unrealistic in vivo. Another common issue with in vitro arsenic studies is that many use short time frames, and very early responses to arsenic do not necessarily reflect in vivo exposures or take into account the adaptive capacities towards arsenic that are generally observed in vivo.

Beryllium and beryllium compounds

Carcinogenicity

There is *sufficient evidence* in humans that beryllium and beryllium compounds cause lung cancer (IARC, 2012). In rats, inhalation of beryllium metal, beryllium sulfate, or beryl ore dust produced bronchiolo-alveolar carcinoma, and intratracheal instillation of beryllium metal, beryllium hydroxide, or beryllium oxide produced bronchiolo-alveolar carcinoma.

Overall, for inhaled beryllium and beryllium compounds, the lung is the one identified cancer target site in humans, a response that has been repeatedly duplicated in rodent models (IARC, 2012).

Mechanisms of carcinogenesis

Multiple, related mechanisms are likely to be operative in beryllium-induced carcinogenesis (IARC, 2012). Although beryllium is inactive or weakly positive as a mutagen, chromosomal aberrations and aneuploidy can occur in vivo in rodents at non-toxic doses. Like many other inorganic carcinogens, beryllium produces oxidative stress, which can lead to damage in DNA or other key biomolecules and then produce gene activation and apoptosis. The cytotoxicity of beryllium in the lung may result in compensatory cell proliferation, along with chronic inflammation. The inflammatory processes induced by beryllium could contribute to the formation of reactive oxygen species, precipitate cell turnover, and activate or disrupt pulmonary cell signalling pathways. Beryllium can decrease DNA repair and recombination. The impairment of DNA repair by beryllium together with increased mitotic signalling may cooperate to induce error-prone cell proliferation (Beyersmann and Hartwig, 2008). The mechanisms of beryllium-induced carcinogenesis are probably complex, multifaceted, and interactive, as with other metals that are human carcinogens (Beyersmann and Hartwig, 2008; Kitchin and Conolly, 2010; Tokar et al., 2010; Brocato and Costa, 2013; Koedrith et al., 2013).

Cadmium and cadmium compounds

Carcinogenicity

There is *sufficient evidence* in humans that cadmium and cadmium compounds cause lung cancer, with positive associations between relevant exposure and cancer of the kidney and prostate (IARC, 2012). In rodents, there is *sufficient evidence* for the carcinogenicity of cadmium and cadmium compounds (IARC, 2012). In rats, inhalation of cadmium chloride, cadmium oxide, cadmium sulfide, or cadmium sulfate produced bronchiolo-alveolar carcinoma or squamous cell carcinoma of the lung, and intratracheal instillation of cadmium chloride and cadmium sulfide both induced primarily bronchiolo-alveolar carcinoma.

Multiple studies in rodents have established that various water-soluble and insoluble cadmium compounds can produce soft tissue sarcomas after repository injections (IARC, 1993, 2012). Studies that produced injection-site tumours have provided some evidence of the carcinogenic potential of cadmium, but there is no concordance with any specific target site in humans. Prostatic proliferative lesions can be produced in rats after oral administration or subcutaneous injection of cadmium chloride.

Overall, cadmium and cadmium compounds are *carcinogenic to humans* and target the lung after inhalation (IARC, 2012). Lung cancers have been repeatedly produced in rodents by either inhalation or intratracheal instillations of cadmium compounds. There is *limited evidence* in humans for prostate and renal carcinogenesis with cadmium or cadmium compounds. In rodents, prostatic proliferative lesions can be induced by cadmium, but there is no concordant evidence in rodents for the kidney.

Mechanisms of carcinogenesis

Cadmium-induced carcinogenesis may be attributable to various mechanisms (Beyersmann and Hartwig, 2008; Brocato and Costa, 2013; Hartwig, 2013; Koedrith et al., 2013). Direct interaction of cadmium with DNA appears to be limited, and cadmium is a weak mutagen. Cadmium can perturb DNA repair and affect tumour suppressor proteins, potentially causing genomic instability and chromosomal damage. Altered DNA methylation patterns

and disrupted signal transduction processes have been observed after exposure to cadmium; these factors could potentially contribute to aberrant cell growth, but their role in cadmium-induced carcinogenesis is unclear. Cadmium can induce reactive oxygen species, but this would be an indirect effect and its precise role in cadmium-induced carcinogenesis is not completely defined. Specific mechanisms of lung carcinogenesis after exposure to cadmium have not been elucidated fully. As with the other inorganic human carcinogens, the mechanisms of cadmium-induced carcinogenesis are probably multifaceted (Beyersmann and Hartwig, 2008; Brocato and Costa, 2013; Koedrith et al., 2013).

Chromium(VI) compounds

Carcinogenicity

There is *sufficient evidence* in humans for the carcinogenicity of chromium(VI) compounds, which cause cancer of the lung (IARC, 1990, 2012). Most of the epidemiological data come from occupational settings that would involve inhalation as the primary route of exposure. Also, positive associations have been observed between exposure to chromium(VI) compounds and cancer of the nose and nasal sinuses (IARC, 2012). In rodents, there is *sufficient evidence* for the carcinogenicity of chromium(VI) compounds (IARC, 1990, 2012). Calcium chromate induced lung tumours (adenomas) in mice, but only when data from male and female groups were combined (Nettesheim et al., 1971). The sex of a test animal is considered by IARC as a quantitative aspect of a tumour end-point study that potentially affects the outcome in terms of chemically induced tumours (IARC, 2012), and therefore the combination of data from male and female animals may be problematic. Male rats chronically exposed by inhalation to sodium dichromate developed lung tumours in one study, although the Working Group for that *Monograph* cautioned about small group sizes in that study (IARC, 1990). Nasal papilloma occurred after chronic inhalation of chromium trioxide in female mice in one study (IARC, 1990). Various compounds of chromium(VI), including calcium chromate, strontium chromate, and zinc chromate, produced local squamous cell carcinoma in rats when the test agent was first mixed with cholesterol and then used to fill or coat stainless steel wire baskets that were subsequently surgically implanted via tracheotomy into the bronchus (IARC, 1990). The coated basket acts as a point of release for the test agent. Implantation of a basket containing cholesterol alone caused notable squamous metaplasia (7% of controls) and bronchial inflammation (89% of controls), indicating that chronic, not agent-related, irritation is involved with this model even without a test agent. Although the tumours induced by this technique of exposure via implantation of a wire basket were histologically defined as bronchiolar squamous cell carcinoma, their relevance to human lung cancer induced by inhalation of chromium(VI), or in fact by any other agent, has not been rigorously validated. Repeated weekly intratracheal instillations of calcium chromate or sodium dichromate in male and female rats produced bronchiolo-alveolar carcinoma and squamous cell carcinoma in one study (Steinhoff et al., 1986). The authors noted that the chromium(VI)-induced tumours coexisted with extensive treatment-related scarring (confluent fibrosis) and chronic inflammatory changes indicative of high tissue burdens of the test agent and local toxicity.

Many studies have demonstrated carcinogenic activity for various chromium(VI) compounds in rodents, such as production of soft tissue sarcomas after repository injections (IARC, 1990, 2012). Studies that produced injection-site tumours have provided some evidence of the carcinogenic potential of chromium (VI), but there is no concordance with any specific target site in humans. Sodium dichromate dihydrate in drinking-water caused adenocarcinoma of the small intestine in mice and squamous cell carcinoma of the oral mucosa and tongue in rats (National Toxicology Program, 2008), but these tissues are not considered cancer target sites in humans. Given the response and the rarity of these tumours in rodents and the potential for oral exposure of humans to chromium(VI), these sites deserve additional focus in epidemiological studies.

The lung is a target site for the carcinogenic effects of chromium(VI) compounds in humans (IARC, 1990, 2012). From inhalation studies in rats and mice, there is *sufficient evidence* that chromium(VI) induces lung tumours, although all the available studies are considered to have some limitations (IARC, 1990). Lung tumours produced by surgically implanting stainless steel wire baskets containing chromium(VI) compounds in cholesterol into the bronchus of rats, like injection-site tumours, probably reflect carcinogenic activity, but the relevance of this exposure technique in modelling tumours produced in humans by inhalation of chromium(VI) compounds requires

further validation. Repeated intratracheal instillations of certain chromium(VI) compounds can produce malignant lung tumours (Steinhoff et al., 1986). There is *limited evidence* that the nose or the nasal sinuses are target sites for the carcinogenic effects of chromium(VI) in humans (IARC, 2012), and one study in mice showed nasal papillomas induced by inhalation of chromium(VI) (IARC, 2012).

Generally speaking, chromium(VI) compounds do show concordance between humans and rodents for the established target site in humans, the lung, on the basis of: (i) two positive inhalation studies in rodents, both with noted limitations (IARC, 1990); (ii) lung tumours induced in rodents by repeated intratracheal instillations; and (iii) activity in a rodent model with surgical implantation of wire baskets containing chromium(VI) compounds into the bronchus to produce lung tumours. However, additional state-of-the-art studies in experimental animals with inhaled chromium(VI) compounds appear to be needed. A high-quality, contemporary tumour end-point inhalation study in rodents would add greatly to the understanding of chromium(VI)-induced carcinogenesis and could be designed to significantly aid in elucidation of the mode of action of this compound (Proctor et al., 2014). Such a study is lacking, presumably because the agent had already been declared a human carcinogen and rodent research resources were directed elsewhere.

Mechanisms of carcinogenesis

In terms of general mechanisms, during in vitro conversion of chromium(VI) to chromium(III) by cellular reductants, various toxic intermediates, including radicals of chromium, oxygen, and sulfur, are likely to be generated, and they can react with key biomolecules relevant to carcinogenesis (IARC, 2012; Hartwig, 2013; Proctor et al., 2014). Some chromium(VI) reductants undergo Fenton-type reactions to produce hydroxyl radicals, which attack DNA. Chromium(VI) can stimulate formation of superoxide and nitric oxide in vitro. Chromium(VI) metabolites can be directly genotoxic, and the metal also causes inflammation and stimulates tumour growth pathways in cell culture systems. Aneuploidy has been observed after exposure to chromium(VI). Significant DNA methylation changes could be a contributing factor in chromium(VI)-induced carcinogenesis, particularly in the lung (Brocato and Costa, 2013). As with other inorganic human carcinogens, it is likely that multiple, probably interactive, mechanisms are operative in chromium(VI)-induced carcinogenesis, including DNA damage, oxidative stress, and aneuploidy, which lead to the acquisition of a malignant phenotype.

Nickel and nickel compounds

Carcinogenicity

There is *sufficient evidence* that mixtures of nickel compounds and metallic nickel cause cancers of the lung, nose and nasal cavity, and paranasal sinuses in humans (IARC, 2012). Epidemiological studies provided evidence for induction of lung cancer by specific nickel compounds, including water-soluble and insoluble substances. In rats, inhalation of nickel oxide, nickel subsulfide, or nickel carbonyl caused bronchiolo-alveolar carcinoma of the lung, whereas intratracheal instillation of nickel oxide, nickel subsulfide, or metallic nickel caused squamous cell carcinoma of the lung. In several well-performed experiments, the inhalation of various nickel compounds, both water-soluble and insoluble, including metallic nickel (in rats), nickel sulfate (in rats and mice), and nickel subsulfide (in mice) did not cause lung tumours. Oral exposure to nickel sulfate did not cause tumours in rats or mice.

Various water-soluble and insoluble nickel compounds and metallic nickel produced various types of sarcomas in rats, mice, or hamsters when administered by repository injections (subcutaneous, intramuscular, intraperitoneal, etc.) (IARC, 2012). Studies that produced injection-site tumours have provided some evidence of the carcinogenic potential of nickel and nickel compounds, but there is no concordance with any specific target site in humans.

There are multiple studies in rodents that recorded increased pheochromocytoma of the adrenal medulla after inhalation of nickel compounds, including metallic nickel and nickel subsulfide (IARC, 2012). These studies might imply the systemic bioavailability of inhaled nickel compounds, although there are no concordant data concerning the adrenal gland as a target of nickel-induced carcinogenesis in humans.

Overall, for nickel and nickel compounds, target site concordance exists between the human lung and the rodent lung for various nickel compounds and metallic nickel. There are no data in rodents on cancers of the nose, nasal cavity, and paranasal sinuses that would be concordant with data in humans.

Mechanisms of carcinogenesis

The nickel ion Ni(II) is considered to be the ultimate carcinogenic species in nickel-induced carcinogenesis (Beyersmann and Hartwig, 2008; IARC, 2012). Water-soluble and poorly water-soluble nickel compounds both enter the cell and reach the nucleus, although the soluble compounds do this by ion channels and transporters, whereas the poorly soluble compounds are taken up by phagocytosis. After phagocytosis, particulate nickel compounds gradually release nickel ions, making them available for interaction with key biomolecules. An increased level of nickel in the nucleus is evident after exposure to water-soluble or insoluble nickel compounds. Nickel compounds are weakly mutagenic in mammalian cells but induce DNA damage, chromosomal aberrations, and micronuclei in vitro and in vivo. Both water-soluble and insoluble nickel compounds induce malignant cell transformation in vitro. However, delayed mutagenicity and chromosomal instability have been observed long after treatment of cells with nickel. Nickel compounds induce epigenetic changes, including alteration in DNA methylation patterns and modification of histones (Brocato and Costa, 2013). An inflammatory component is also thought to contribute to nickel-induced carcinogenesis. Direct effects of nickel on DNA are probably limited, but oxidative stress and oxidative DNA damage have been found after nickel exposure. As with the other inorganic human carcinogens, it is likely that multiple, potentially interdependent, complex mechanisms are operative in nickel-induced carcinogenesis.

Comparative mechanisms of the inorganic human carcinogens

Among arsenic compounds and metals that are human carcinogens, only chromium(VI) seems to have the ability to interact with DNA directly, at least when it undergoes intracellular reduction, and to act as a direct genotoxin. Chromium(VI) does show human-to-rodent target site concordance with respect to the lung, although up-to-date inhalation studies in rodents would greatly aid in defining the mechanisms of chromium(VI)-induced carcinogenesis (see above; Proctor et al., 2014). With the inorganic human carcinogens other than chromium(VI), direct induction of DNA damage is not a key mechanism. All the metals that are human carcinogens seem to be able to cause oxidative stress (Beyersmann and Hartwig, 2008; Hartwig, 2013), mostly by indirect means. This may contribute to their carcinogenic potential because the resulting oxidative species could attack DNA. Arsenic, cadmium, chromium, and nickel can have epigenetic effects on DNA that alter critical gene expression and promote the acquisition of a malignant phenotype (Brocato and Costa, 2013).

With respect to carcinogenesis induced by inorganic chemicals, it is generally accepted that the ionic species is the most active species for the metals that are human carcinogens (i.e. beryllium, cadmium, chromium(VI), and nickel) (IARC, 2012). However, this scenario is not likely to be entirely true for the metalloid arsenic and its compounds. Of all the inorganic human carcinogens, inorganic arsenic alone can undergo conjugative biotransformation within the host. Methylation of inorganic arsenic generally produces monomethylarsenic (MMA) forms and then dimethylarsenic forms, but this process is not complete in most people (Melak et al., 2014). Incomplete methylation can result in the formation of very toxic, monomethylated arsenic metabolites, like MMA(III). Recent data in humans indicate that an increased MMA level, as a percentage of total urinary arsenic, strongly correlates with cancer of the lung and bladder in a population in northern Chile exposed to environmental inorganic arsenic (Melak et al., 2014). This indicates that arsenic metabolites generated by incomplete methylation are associated with increased carcinogenic risk after exposure to inorganic arsenic.

Stimulation of inflammation is also common among the group of inorganic human carcinogens. The role of inflammation in carcinogenesis may be secondary, through provision of oxidants or radical species produced by oxidation.

Definitive mechanisms have not been established for any inorganic human carcinogen. These agents are best considered to be multifaceted, interrelated, and complex carcinogens. For the inorganic carcinogens with multiple target sites, there is a strong possibility that the mechanism is target site-specific.

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