Review Paper

A Review of Genetic and Epigenetic Mechanisms in Heavy Metal Carcinogenesis: Nickel and Cadmium

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Abstract. Heavy metals constitute an important class of environmental contaminants that classified as human carcinogens according to the US Environmental Protection Agency and the International Agency for Research on Cancer. They affect human health through occupational and environmental exposure. Multiple experimental epidemiological studies indicate that heavy metals such as Nickel and Cadmium can induce several types of cancer significantly pulmonary cancers, but the mechanisms underlying the carcinogenesis are not well understood yet. This metals are genotoxic elements for human, while they are typically weak mutagens, indicating that indirect mechanisms may be primary responsible for their genotoxicity. Several studies suggest that epigenetic mechanisms may play an important role in metal-induced carcinogenesis. Here, we review studies that investigate the common mechanisms of nickel and cadmium-induced carcinogenesis, include DNA methylation, histone modification, induction of oxidative stress, interference with DNA repair system, and interruption of cell growth and proliferation through signaling pathway and dysregulation of tumor suppressor genes.

Key words: Nickel, Cadmium, Genotoxicity, Molecular mechanism

1. INTRODUCTION

Pollution of the biosphere with heavy metals due to man-made activities poses an important environmental and human health problem (Kabir et al., 2012; Han et al., 2002; Gavanji et al., 2012). Increasing data show a link between heavy metal exposure and aberrant changes in both genetic and epigenetic factors in humans. Nickel and cadmium are heavy metals which exposure to their compounds can induce several kinds of cancers specially pulmonary cancer (Grimsmrud et al., 2003; Waalkes, 2000; Gavanji et al., 2013). Exposure of Syrian hamster embryo (SHE) cells to nickel subsulfide resulted in morphological transformation and the transformed cells were able to induce sarcomas in nude mice. Also the exposure of mouse embryonic fibroblast C3H/10T 1/2 cells to nickel sulfide also led to cell transformation (Salnikow and Costa, 2000). It has been shown that cadmium can induce malignant transformation of the human prostate epithelial cell line (RWPE-1) (Achanzar et al., 2001). Molecular mechanisms underlying Ni and Ca cell-transforming ability are not well understood. Both of them are weak mutagens and do not exhibit positive effects in a wide range of mutation tests (IARC, 2012). Thus Several types of indirect mechanisms have been identified that may contribute to their genotoxic potentials, such as induction of oxidative DNA damage and gene silencing by changes in DNA methylation patterns (Aritaa and Costa, 2009).

2. METHODOLOGY

Firstly, based on our research about heavy Metal, articles regarding to effects of heavy Metal on eukaryotic cells were searched in several data bases available through UI (University of Isfahan) library website and Google scholar too. Referral articles (150 articles) include which were published between 1981 to 2013. Then they were reviewed during 8 months and important points related to the effect of heavy Metal on eukaryotic cells were studied particularly. We, in this review, studied the molecular mechanism of heavy Metal on eukaryotic cells.

2.1. Nickel

Nickel is a hard, silvery-white transition metal with the atomic number 28. It is the 24th most abundant element. The most important oxidation state of nickel is +2. Other valences include -1, 0, +1, +3 and +4 (Tundermann et al., 2005). Nickel and its compounds are widely used in modern industry. It is used in conjunction with other metals to form alloys to produce coins, jewelry, and stainless steel as well as for nickel plating and manufacturing Ni-Cd batteries and for catalyze the production of carbon nanoparticles (Grandjean, 1984). The production,
processing, and recycling of nickel products has resulted in a high level of pollution such that nickel contamination now occurs in water, soil and the ambient air (Lippmann et al., 2006). Combustion of fossil fuels produces the greatest contribution of nickel compounds in the ambient air (Merian, 1984). Nickel compounds can enter the body through inhalation, ingestion, and dermal absorption (Grandjean, 1984) and they have been found to be carcinogenic based upon numerous epidemiological studies (Doll et al., 1970). The International Agency for Research on Cancer (IARC) evaluated the carcinogenicity of nickel in 1990. All Ni (II) compounds were recognized as human carcinogens (Group 1) and metallic nickel is classified as possibly carcinogenic to humans (Group 2B) (Kasprzak et al., 2003). It has been found that exposures to nickel compounds are associated with increased nasal and lung cancer incidence (Andersen, 1996; Grimsmud et al., 2003). A summary of toxicity of various nickel species and compounds are shown in table 1. The carcinogenicity of nickel has been explained by several mechanisms such as inhibition of DNA repair (Woźniak and Błasiak, 2008) which are discussed below.

2.2. Cellular uptake

Carcinogenesis of metal compounds depends on their ability to enter the cell and it’s probably related to their solubility in water. Water-soluble nickel compounds possess lower toxic and carcinogenic potential as compared to insoluble nickel compounds because Water-soluble compounds such as Nickel acetate, bromide, chloride, iodide, nitrate and sulfate are quickly flushed from tissue and therefore has a limited ability to enter the cell via the divalent metal transporter 1 (DMT1) (Funakoshi et al., 1997; Denkhaus and Salnikow, 2002). Some of soluble nickel compounds enters cell via calcium channels (Refsvik and Andreassen, 1995; Funakoshi et al., 1997). NiCl2 and NiSO4 enter cells with relative ease, possibly following conjugation with serum proteins or amino acids such as histidine (Costa et al., 1981). Insoluble nickel compounds possibly enter the cell through phagocytosis. many results clearly indicate that water-insoluble nickel compounds such as crystalline nickel sulfide(Nis) and crystalline nickel sub sulfide(Ni3S2) phagocytized by a large variety of different cells in culture (Costa et al., 1981). Ni carbonyl, a highly toxic form of Ni, is lipid soluble allowing it to pass through the cellular membrane and in turn significant absorption occurs through inhalation and skin contact (Muñoz and Costa, 2012).

Numerous studies point to the cell nucleus as the site of nickel attack (Salnikow et al., 1994; Lee et al., 1995). Nickel chloride has been shown in different cell lines in culture to be transported to the nucleus (Edwards et al., 1998; Schwerdtle and Hartwig, 2006).

2.3. Induction of oxidative stress

Nickel compounds are able to cause the cell transformation and chromatin damage (Cai and Zhuang, 1999; M’Bemba-Meka et al., 2005) but they are not mutagenic in a wide range of bacterial mutagenesis assays and are only weakly mutagenic in cultured mammalian cells (Biggart and Costa, 1986; Klein et al., 1991; Kerckaert et al., 1996). One possible explanation for this is nickel cause the DNA damage and cell transformation via generation of reactive oxygen species (ROS) (Salnikow and Costa, 2000). Like many other carcinogenic metals, nickel compounds are able to induce the formation of ROS. Nickel is a reduct-oxide metal that can catalyse Fenton-type reactions (Huang et al., 1993; Chen et al., 2003). In cells treated with nickel compounds, increase in DNA stand breaks, DNA–protein crosslinks and sister chromatid exchange was observed and these are shown to result from the increase in reactive oxygen species (Chakrabarti et al., 2001; M’Bemba-Meka et al., 2005, 2007). Nickel (II) ions can catalyze the generation of OH radicals from H2O2. These radicals attack the DNA bases and cause to formation of typical OH-induced products of DNA bases in isolated human chromatin (Nackerdien et al., 1991; Lloyd and Phillips, 1999).

2.4. Inhibition of DNA repair

There is accumulating evidence that carcinogenic nickel compounds disturb DNA repair systems by diverse mechanisms. Ni (II) disturbed the first step of nucleotide excision repair (NER), that involves recognition of damaged DNA (Hartmann and Hartwig, 1998). It had found that repair inhibition by Ni (II) may be caused by the displacement of zinc in zinc finger structures of DNA repair proteins such as XPA protein (Asmuss et al., 2000a). There is some evidence that Ni (II) inhibits the repair of O6-methylguanine via silencing of the DNA repair gene O6-methylguanine DNA methyltransferase (MGMT) expression (Jiwitzki et al., 1998; Ji et al., 2008). Soluble nickel chloride also inhibits base excision repair (BER), via inhibition the base-excision repair enzyme, 3-methyladenine-DNA glycosylase II (Dally and Hartwig, 1997; Wang et al., 2006). Nickel Inhibition of DNA Repair may be mediated by Reactive Oxygen Species. Ni enhances the intracellular H2O2 level, which may increase
oxidative damage in DNA repair enzymes and thereby reduce this enzymes activity (Lynn et al., 1997; Gavanji et al., 2013). Nickel Ions Inhibit DNA Repair Enzyme ABH2 and Histone Demethylase JMJD1A. These enzymes are iron- and 2-oxoglutarate-dependent dioxygenases that uses the 2-His-1-carboxylate motif to bind the cofactor ferrous iron ion at their active sites. Ni (II) competes with Fe(II) and replaces it at the iron-binding site thus inhibit enzyme activity (Chen et al., 2010).

2.5. Epigenetic mechanisms, gene silencing and Deregulation of cell proliferation

The epigenetic dysregulation of gene expression is one of primary causes in cancer (Egger et al., 2004; Ke et al., 2006). Silencing of tumor suppressor genes by epigenetic mechanisms represents one of the main mechanisms of nickel carcinogenesis. Both watersoluble and water-insoluble nickel compounds are able to cause gene silencing via diverse epigenetic mechanisms (Costa et al., 2005). Nickel inactivates transcription of genes by inducing DNA methylation and chromatin compaction (Lee et al., 1995). So it seems that Heterochromatinization is a potential mechanism of nickel-induced carcinogenesis (Ellen et al., 2009). Nickel compounds cause posttranslational epigenetic modifications of histone proteins, thus derailing the normal programming of gene expression (Sutherland and Costa, 2003; Zhou et al., 2009). It has been shown that the transcriptional suppression of MGMT (O6-methylguanine DNA methyltransferase) expression in NiS-transformed cells mediate by epigenetic Histone modifications at the promoter region of MGMT gene (Ji et al., 2008). Recently, Arita et al, demonstrated that exposure to nickel compounds, can induce changes in global levels of posttranslational histone modifications in peripheral blood mononuclear cells (Arita et al., 2012). Recent studies show that cells treated with nickel have decreased histone acetylation, and altered histone methylation patterns (Broday et al., 2000; Sutherland and Costa, 2003; Chen et al., 2006). Nickel exposure increased the level of H3K4 trimethylation in both the promoters and coding regions of several genes including CA9 and NDRG1 that were increased in expression in A549 cells (Tchou-Wong et al., 2011). It also increased lysine 9 in histone H3 (H3K9) dimethylation by inhibiting the demethylating enzyme JHDM2A (Chen et al., 2010). Nickel is a potent inhibitor of histone H4 acetylation in yeast and in mammalian cells (Broday et al., 2000). The loss of histone acetylation and DNA methylation worked together in gpg gene silencing in G12 transgenic cell line by nickel (Zoroddu et al., 2002; Yan et al., 2003). Nickel also causes ubiquination and phosphorylation of histones (Karaczyn et al., 2006; Ke et al., 2008). Nickel ions may deregulate cell proliferation by inactivating apoptotic processes. P53 is an important tumor suppressor gene and transcription factor which involved in the regulation of cell proliferation and apoptosis (Bates and Vousden, 1999). Nickel ions inhibit binding of p53 to scDNA and to its consensus sequence in linear DNA fragments (Palecek et al., 1999). In another study it was observed that nickel-immortalized cells revealed abnormal p53 expression and a T–C transition mutation in codon 238 (Maehe et al., 1992). The Fragile Histidine Triad (FHIT) gene is a tumor suppressor gene that locates in a fragile chromosomal site sensitive to deletions. in tumors the expression of FHIT gene was frequently found to be reduced even lost (Kasprzaker et al., 2003). It was found in vitro that Ni (II) had strong inhibitory effect on the enzymatic activity of Fhit protein. Also in nickel-induced tumors, aberrant transcripts or loss of expression of the FHIT gene and Fhit protein was observed (Kowara et al., 2002; Ji et al., 2006). It appears that amplification of certain oncogenes is a common correlate of the progression of some nickel induced tumors and cancers (Sunderman et al., 1990). Elevated expression of oncogenic c-myc mRNA was reported in nickel transformed mouse 10Ti1/2 cells (Landolph, 1994). In the past few years, many studies have been conducted on the molecular mechanisms of nickel carcinogenesis which focused on the activation of proto-oncogenes and inactivation of anti-oncogenes caused by gene amplification, DNA methylation, chromosome condensation, and so on that were induced by nickel. However, the researches on tumorigenic molecular mechanisms regulated by microRNAs (miRNAs) are rare. By establishing a cDNA library of miRNA from rat muscle tumor tissue induced by Ni3S2, Zhang et al (2013) found that the expression of miR-222 was significantly up regulated in tumor tissue compared with the normal tissue. They concluded that miR-222 may promote cell proliferation infinitely during nickel-induced tumor genesis in part by regulating the expression of its target genes CDKN1B and CDKN1C.

2.6. Cadmium

Cadmium (atomic number, 48; relative atomic mass, 112.41) is a heavy metal that belongs to group IIB of the periodic table. The oxidation state of about all cadmium compounds is +2, although a few compounds have been reported in that it is +1. (IARC, 1993). Cadmium (cd) is a toxic transition metal that has been designated a human carcinogen by the National Toxicology program. Cadmium found naturally in ores together with zinc, lead and copper.
Sources of human exposure to cadmium include certain batteries manufacturing, some electroplating processes and consumption of tobacco products. Multiple epidemiological studies have linked occupational exposure to cadmium with pulmonary cancer, while fewer studies have linked it to prostate, renal, liver, hematopoietic system, urinary bladder, pancreatic, and stomach cancers (Waalkees and Misra, 1996; Waalkes, 2000; Hu et al., 2002). A summary of toxicity of various cadmium species and compounds are shown in table 2. Cadmium is a weak mutagenic and has a poorly DNA binding affinity, suggesting that it promote carcinogenesis through epigenetic mechanisms (Arita and Costa, 2009). suggested mechanisms for Cd-carcinogenesis include such as formation of reactive oxygen species (ROS) and/or interference with anti-oxidative enzymes, inhibition of DNA repair enzymes, deregulation of cell proliferation, suppressed apoptosis (Waalkes, 2003).

### 2.7. Cellular uptake

Investigation of the cellular cadmium uptake mechanism in the rat jejunum showed that, this process is done through nonspecific binding to anionic sites on the membrane, then followed by a temperature –dependent and limiting internalization step (Foulkes., 1989). Hinkle indicated that a major mechanism for cellular uptake of cadmium is dependent to voltage-sensitive calcium channels (Patricia et al., 1987). Studies showed that Mn transport system is used for cellular dc uptake. Divalent metal transporter 1 (DMT1) is the only known mammalian transporter involved in the uptake of both Cd and Mn (Himeno et al., 2002). Exogenous glutathione (GSH) prevent cellular uptake through form a complex with cadmium outside of the cells (Kang, 1992).

### 2.8. Induction of oxidative stress

Cadmium is a bivalent cation and unable to produce reactive oxygen species (ROS) directly, nevertheless cd-induced oxidative estacies reported in multitude studies (Wang et al. 2004, Valko et al. 2005; Zhou et al., 2009). Cadmium sulfide enhanced hydrogen peroxide production in human leukocytes, and cadmium chloride induced the formation of superoxide in rat and human phagocytes (Sugiyama, 1994). Experiments in both in vivo and in vitro, indicated that cadmium has inhibitory effect on antioxidant enzymes through the interaction with their thiol groups (Stohs et al., 2001; Valko et al., 2006; Gavanji et al., 2013). Cadmium also can replace of copper and iron in various proteins, and hence increase the cellular amount of free redox-active metals (Price and Joshi, 1983; Dorta et al., 2003).Cd-exposed for long-term enhanced lipid peroxidation and inhibited activity of superoxide dismutase (SOD) in rat liver, kidney and testes (Patra et al., 1999). Investigation of cadmium-effects on basic motility characteristics in bovine seminal plasma and spermatozoa, shown that cadmium can increase the development of oxidant stress so decrease of male fertility (Tvrdá, 2013).

### 2.9. Inhibition of DNA repair

Cadmium also exert comutagenic effects, by disturbances several types of DNA-repair mechanisms, i.e. base excision, nucleotide excision, mismatch repair, and the exclusion of the pre-mutagenic DNA precursor 7,8-dihydro- 8-oxoguanine (Hartwig and Schwerdtle, 2002). In base-excision repair, sub-lethal concentrations of cadmium do not generate oxidative damage as such, but suppress the repair of oxidative DNA damage in mammalian cells (Dally and Hartwig, 1997; Fatur et al., 2003). Exposure of human cells to cd low concentration decrease removal of x-ray-induced 8-oxoguanin ( 8-oxoG) adducts, that in turn increase the mutation frequency, this occurs through decrease in hOGG1 (human8-oxoguanine-DNA glycosylase-1) activity (Youn et al., 2005; Bravard et al., 2009). Recently studies shown that hOGG1 significantly reduced in the presence of in human spermatozoa (Smith et al., 2013). On analysis dedicated microarray in vitro shown inhibitory effects of cadmium in both base and nucleotide exision/repair pathways (Candéias, 2010). In nucleotide-excision repair, cadmium suppress the removal of thymine dimers after UV irradiation by inhibiting the incision at the DNA lesion (Hartwig and Schwerdtle, 2002; Fatur et al., 2003). Schwerdtle et al. indicated that cadmium compounds such as CdO and soluble CdCl₂ inhibit the nucleotide excision repair in a dose-dependent manner at low concentration (2010). Cadmium suppress the 8-oxo-dGTPases activity, therefore disturbs the exclusion of 8-oxo-dGTP, a product of oxidative modification of dGTP, from the nucleotide pool (Bialkowski and Kasprzak, 1998). Additionally cd can displace the zinc in DNA-repair proteins such as xerodermapigmentosum group A (XPA) that is involved in nucleotide-excision repair and inhibit their function (Asmuss et al., 2000b). Recent evidence suggests that existence of Microsatellite instability, one of the phenotypes of defective DNA mismatch repair, in nuclear indicating genotoxic effects induced by cadmium (Oliveira et al., 2012).
2.8. Epigenetic mechanisms, gene silencing and Deregulation of cell proliferation

Most studies indicate cadmium is poorly mutagenic, and has a weak DNA binding affinity, so probably promote carcinogenesis through indirect or epigenetic mechanism including aberrant activation of oncogenes and suppression of apoptosis (Waalkes, 2003; Arita and Costa, 2009). Multiple studies are shown that cadmium can induce epigenetic effects in experiment
animals and mammalian cells in vitro (Martinez-Zamudio and Ha, 2011; Wang et al., 2012; Waalkes, 2003; DFG, 2006). Several studies have reported that cadmium can induce changes in global and gene specific DNA methylation levels (Takiguchi, 2003; Benbrahim-Tallaa, 2007; Huang, 2008). Cd can alter the epigenetic programming in chick embryos through down regulation of DNA methyltransferases and following diminishment of DNA methylation (Doi et al., 2011). In vitro and ex vivo experiments shown that cd inhibit DNA methyltransferase (MeTase) in a noncompetitive manner with DNA, possibly through an interaction with the methyltransferase DNA binding domain (Takiguchi et al., 2003). Gene-specific DNA hypermethylation and gene silencing have been reported in cadmium-exposed cells, including the p16INK4a, RASSF1A and MT-1 genes (Takiguchi et al., 2003; Benbrahim-Tallaa et al., 2007). It has been proposed that the teratogenic effect of Cd could also be mediated by epigenetic mechanisms, because altered DNA methylation has been linked to ventral body wall defect (VBWD) in chick embryos after Cd treatment (Doi et al., 2011; Menoud and Schowing., 1987; Thompson and Bannigan, 2001). These data suggest that Cd may act as a teratogen to induce VBWD by perturbing DNA methylation. Benbrahim reported that cadmium exposure During the 10-weeks induced malignant transformation, increased activity DNA methyltransferase (DNMT) that were associated with over-expression of DNMT3b. This pattern DNA hypermethylation together with up-regulation of DNMT3b may provide biomarkers to specifically identify cadmium-induced human prostate cancers (Benbrahim-Tallaa et al., 2007). Cd – exposed human embryo lung fibroblasts (HLF) increase both global DNA methylation and DNMT activity. Also significantly elevated growth rates of the HLF cells, decreased cell population of G0/G1-phase and increased cell population of S-phase (Jiang et al., 2008). Another study Using K562 cells (chronic myelogenous leukemia cell line), showed that Cd stimulated cell proliferation did not suppress in the attenuation of ROS generation with N-acetylcysteine (Huang et al., 2008). However, methionine could suppress Cd-induced global DNA hypomethylation and cell proliferation. It was concluded by the authors that global DNA hypomethylation, rather than ROS, is the potential facilitator of Cd-stimulated K562 cell proliferation. Recently studies indicate that cd-exposed DNA methylation in early life is sex-specific and related to lower birth (Kippler, 2013). Exposure to Cd induce the hypermethylation of RASAL1 and KLOTHO, associated-genes with renal fibro genesis, suggest that this pattern may be an epigenetic marker of the progress for chronic kidney disease (Zhang et al., 2013). Epigenetic changes in expression of MT-3 were studied in human breast epithelial cancer cells (Somji et al., 2011). These studied showed that the MT-3 gene is silenced by histon modification of the MT-3 promoter. Cadmium affects multitude cellular processes, including signal transduction pathways, cell proliferation, differentiation, and apoptosis. At Submicromolar concentrations, cadmium stimulated cell growth and DNA synthesis, and the proliferation of rat myoblast, epithelial and chondrocyte cells (Zglinicki et al., 1992) and of rat macrophages (Misra et al., 2002). Cadmium decreased level of estrogen receptor and other estrogen-regulated genes in human breast cancer cell line MCF-7, and induced the growth of these cells 5-6 fold (Garcia-Morales et al., 1994). Cadmium exposure also increased uterine weight and density of the mammary gland and induced tumorigenesis in the lining of the uterus (Johnson, 2003). Cadmium-induced apoptosis occurs by Caspase-9 activation triggered by cytochrome-c in human promyelocytic Leukemia HL-60 cells (Kondoh et al., 2002) or through reactive oxygen species (ROS) pathway and translocation of apoptosis-inducing factor (AIF) from mitochondria into the nucleus (Shih., 2004). Recently studies showed that cadmium induce P53-dependent apoptosis in human prostate epithelial cells (Aimola et al., 2012). Cadmium elevates intracellular free calcium ion ([Ca2+]i) level, leading to neuronal apoptosis partly by activating mitogen-activated protein kinases (MAPK) and mammalian target of rapamycin (mTOR) pathways (Xu et al., 2011). Several studies have shown that cadmium in addition to stimulating mitogenic directly, indicate the negative controls of cell proliferation. Subtoxic levels of cadmium can suppress the P53-dependent cell cycle arrest in G(1) and G(2)/M phases induced by gamma-irradiation through conformational changes of wild-type P53(Méplan et al., 1999). It was reported that Cd reduce and inactive expression of the tumor suppressor genes, RASSF1A and P16, through over expression of de novo DNA methyltransferase (Benbrahim et al., 2007). Recently, Cd has been shown to enhance estrogen receptor alpha activity and stimulate uterine and mammary gland growth in mic and plays an important role in the promotion of breast cancer (Siewit et al., 2010).

3. RESULTS AND DISCUSSION

During the past centuries, commercial and industrial use of heavy metal compounds increased, and the progress of industrialization has led to increased emission of pollutants into ecosystems (Järup, 2003). The potential anthropogenic heavy metal inputs in the pedosphere increased tremendously after the 1950s. In 2000, the cumulative industrial age anthropogenic
global production of Cd and Ni was 1.1 and 36, million tons (Fengxiang et al., 2002). The evidence described above demonstrates that exposure to nickel and cadmium compounds can disturb multitude cellular processes, including signal transduction pathways, cell proliferation, and apoptosis. The mechanisms underlying this effects are not well understood yet, but three predominant mechanisms have been identified to explain Ni and Cd toxicity and carcinogenicity: (1) interference with cellular redox reactions and induction of oxidative stress, which may cause oxidative DNA damage (Chen et al., 2003; Stohs et al., 2001); (2) inhibition of DNA repair systems resulting in genomic instability and accumulation of critical mutations(Hartmann and Hartwig., 1998; Fatur et al., 2003); (3) deregulation of cell proliferation by induction of signaling pathways or inactivation of growth controls such as tumor suppressor genes (Palecek et al., 1999; Méplan et al., 1999). Zhang et al (2013) identified a novel molecular mechanism of nickel-induced tumorigenesis which regulated by microRNAs (miRNAs). They stated that miR-222 may promote cell proliferation infinitely during nickel-induced tumorigenesis in part by regulating the expression of its target genes CDKN1B and CDKN1C. Some recent studies have suggested that Cadmium and nickel play a role in breast cancer development by acting as metalloestrogens--metals that bind to estrogen receptors and mimic the actions of estrogen (Martin et al., 2003). Aquino et al, have discussed the various epidemiological, in vivo, and in vitro studies that show a link between the heavy metals, cadmium and nickel, and breast cancer development, in a review article in 2012. One of the potential mechanisms for nickel induced carcinogenesis is mediated by reactive oxygen species resulting oxidative stress. Nickel is a redox-active metal that can catalyse Fenton-type reactions (Chen et al., 2003). Unlike the nickel, cadmium is a non-redox metal therefore unable to produce reactive oxygen species directly (Wang et al., 2004). But it can induce generation of ROS through inhibitory effect on antioxidant enzymes by interaction with their thiol groups (Valko et al., 2006). Cadmium exhibit remarkable potential to inhibit DNA damage repair, and it has been identified as a major mechanism for its carcinogenicity (Giagenis et al., 2006). In summary, the direct effect of toxic metals on the genes and chromosomes such as DNA damage, mutation and chromosomal aberrations is weak and rare and usually observed at higher concentrations (Hartwig, 1995). Therefore the main mechanism in their carcinogenicity is epigenetic mechanism.

4. CONCLUSION

The aim of this review was to evaluate the potential carcinogenicity and the general mechanism of nickel and cadmium. Genomic mutation studies showed that both nickel and cadmium compounds are very weak mutant. The effects of these heavy metals on human body which were investigated in epidemiological studies and analytical experiments showed the damages in the cells. These damages were caused by the increase of free radicals and stimulation of oxidative stress. Inhibition of DNA repair, and deregulation of cell proliferation by Epigenetic mechanisms.

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Table 2: toxicity and carcinogenicity of various cadmium species and compounds

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
<th>Solubility</th>
<th>Reference</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium</td>
<td>Cd</td>
<td>Insoluble</td>
<td>Person et al, 2013</td>
<td>exposing the peripheral lung epithelia cell line, HPL-1D, to a low level of cadmium</td>
<td>induces cancer cell characteristics in human lung cells</td>
</tr>
<tr>
<td>Cadmium acetate</td>
<td>Cd(CH3COO)2</td>
<td>Soluble</td>
<td>Yang, 1998</td>
<td>Exposing Chinese hamster ovary (CHO)-K1 cells to cadmium acetate</td>
<td>decreased the colony-forming ability of cells and induced mutation frequency in the hypoxanthine (guanine) phosphoribosyltransferase (hppt) gene</td>
</tr>
<tr>
<td>Cadmium carbonate</td>
<td>CdCO3</td>
<td>Insoluble</td>
<td>Rusch et al, 1986</td>
<td>Rats exposed for 2 hours to CdCO3</td>
<td>at the higher levels of 132 mg/m3 developed rales, rapid breathing, and 2-3-fold increases in lung weight</td>
</tr>
<tr>
<td>Cadmium chloride</td>
<td>CdCl2</td>
<td>high</td>
<td>Takenaka et al, (1983)</td>
<td>exposed male Wistar rats to cadmium chloride aerosol (MMAD=0.55 μm)</td>
<td>increases in the incidence of lung tumors, including adenocarcinomas, squamous cell carcinomas, and mucoepidermoid carcinomas</td>
</tr>
<tr>
<td>Cadmium nitrate</td>
<td>Cd(NO3)2</td>
<td>high</td>
<td>Dote et al, 2007</td>
<td>intravenous administration of CdN in rats</td>
<td>hyperkalemia associated with renal injury and hepatic damage</td>
</tr>
<tr>
<td>Cadmium stearate</td>
<td>Cd(C36H72O4)</td>
<td>Insoluble</td>
<td>Minoru et al, 1974</td>
<td>cerebellar cells from newborn rat in tissue culture</td>
<td>inhibited the outgrowth of cells and produced degenerative changes at a concentration of 0.58 × 10^{-6} M</td>
</tr>
<tr>
<td>Cadmium sulfate</td>
<td>CdSO4</td>
<td>Soluble</td>
<td>Bassendowska-Karska et al, 1987</td>
<td>sister chromatid exchanges (SCEs) in lymphocytes of human peripheral blood</td>
<td>No significant increase was found in the mean frequency of SCEs in lymphocytes</td>
</tr>
<tr>
<td>Cadmium oxide</td>
<td>CdO</td>
<td>negligible</td>
<td>Sanders and Mahaffey, 1984</td>
<td>intratracheal instillation of 25, 50, or 75 μg cadmium oxide into male F344 rats</td>
<td>induce d mammary gland tumors, but not lung tumors</td>
</tr>
<tr>
<td>Cadmium sulfide</td>
<td>CdS</td>
<td>Insoluble</td>
<td>Glaser et al, 1990</td>
<td>Inhalation exposure to Cadmium sulfide aerosol (90 μg Cd/m^3)</td>
<td>observed lung tumors After 4 weeks</td>
</tr>
</tbody>
</table>
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