Cobalt with tungsten carbide

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Citation for most recent IARC review

IARC Monographs 86, 2006

Current evaluation

Conclusion from the previous Monograph (IARC 2006)

Cobalt metal with tungsten carbide is probably carcinogenic in humans (Group 2A). A number of working group members supported an evaluation in Group 1 because: (1) they judged the epidemiological evidence to be sufficient, leading to an overall evaluation in Group 1; and/or (2) they judged the mechanistic evidence to be strong enough to justify upgrading the default evaluation from 2A to 1. The majority of working group members who

supported the group 2A evaluation, cited the need for either sufficient evidence in humans or strong mechanistic evidence in exposed humans. Cobalt metal without tungsten carbide is possibly carcinogenic to humans (Group 2B). Cobalt sulfate and other soluble cobalt (II) salts are possibly carcinogenic to humans (Group 2B).

Exposure and biomonitoring

Cobalt is widely distributed in the environment, occurring in the earth's crust mainly in the form of sulfides, oxides and arsenides. Cobalt metal is used to make corrosion- and wear-resistant alloys used in aircraft engines (superalloys), in magnets (magnetic alloys) and in high-strength steels and other alloys for many applications. Cobalt metal is added to metal carbides, especially tungsten carbide, to prepare hard metals (two-phase composites; also known as cement carbides) for metal-working tools. Cobalt is also used to manufacture cobalt-diamond grinding tools, cobalt discs and other cutting and grinding tools made from cobalt metal. Other uses of cobalt include catalysts, batteries, dyes and pigments and related applications. Occupational exposure to cobalt occurs predominantly during the refining of cobalt, in the production of alloys, and in the hard-metal industry where workers may be exposed during the manufacture and maintenance of hard-metal tools and during the use of diamond-cobalt tools.

Exposures

The epidemiological evidence to date comes from hard-metal industry and cobalt production. Exposure to hard-metal dust takes place at all stages of the production of hard metals, but the highest levels of exposure to cobalt have been reported to occur during the weighing, grinding and finishing phases (Reber and Burckhardt 1970, McDermot 1971, NIOSH 1981, Sprince et al., 1984, Hartung 1986, Kusaka et al., 1986, Balmes 1987, Meyerbisch et al., 1989, Auchincloss et al., 1992, Stebbins et al., 1992). For example, in two factories in the USA producing hard metals, peak cobalt concentrations in air during weighing, mixing and milling exceeded 500 $\mu g/m^3$ in more than half of all samples (Sprince et al., 1984), and in powder rooms with poorly-regulated control of cobalt dusts, concentrations of cobalt in air ranged from between 10 $\mu g/m^3$ and 160 $\mu g/m^3$ (Auchincloss et al., 1992).

Cobalt concentrations in air were determined for all stages in the manufacturing process in Japan (Kusaka et al., 1986, Kumagai et al., 1996). The concentrations of cobalt were shown to be lognormally distributed and the geometric means for the different workshops ranged from 2 $\mu g/m^3$ in blasting and electron discharging to 211 $\mu g/m^3$ in rotation in powder prevention to 233 $\mu g/m^3$ in rubber press.

Several studies exist that have examined cobalt concentrations in urine. Notable among these were a study of hard-metal workers in several small factories in northern Italy. Cobalt concentrations in the urine of six operators on machines without aspirators were up to 13 times higher than those in the reference population (Cereda et al., 1992). A British study reported median concentrations of cobalt in urine of 19 nmol/mmol creatinine in workers in the hard-metal industry and 93 nmol/mmol creatinine in workers manufacturing and handling cobalt powders, salts and pigments in the chemical industry (White and Dyne 1992).

Concentrations of different tungsten species (W, WC, WO, WO_4^{2-}) were studied in air and in urine samples from workers in different areas in a hard-metal factory in Germany (Kraus et al., 2001).

Cancer in humans

(*limited evidence***,** Vol 86, 2006)

The current epidemiological evidence falls just short of providing convincing evidence for a carcinogenic effect of exposure to cobalt with tungsten carbide in humans.

There have been no relevant epidemiological studies since the most recent monograph was published. The current epidemiological evidence comes from a small nested case-control in the French hard-metal industry (Moulin et al., 1998) and a smaller study in the Swedish hard-metal industry (Hogstedt and Alexandersson 1990).

Cancer in experimental animals

No new experimental animal studies involving cobalt without tungsten carbide were found since the last IARC review (IARC 2006).

De Boeck et al. (De Boeck et al., 2003) studied the effects of a single intratracheal instillation of tungsten carbide-cobalt (WC-Co) particles on rat type II pneumocytes using the alkaline comet assay and micronucleus tests using a dose response /time course protocol. The comet assay was also conducted on cells recovered by broncho-aveolar lavage (BAL) and on peripheral blood mononucleated cells (PBMC). Direct lung toxicity was evaluated by group of standard toxicity markers. The results of these studies indicated that the WC-Co particle exposure produced a statistical increase in DNA comet tails at 12 hours and in micronuclei at 72 hours in the type II pneumocytes at a dose level that produced only mild lung toxicity. No effects were observed in the PMBC. These data provide evidence of WC-Co particle mutagenic potential in a lung target cell population following in vivo exposure.

Mechanisms of carcinogenicity

Cobalt

An extensive and growing literature on molecular mechanisms of cobalt cellular toxicity has been published since the last IARC review. Cobalt induced formation of reactive oxygen species (ROS) leading to a number of molecular effects related to oxidative stress have been document in cellular test systems. Studies by De Boeck et al. (De Boeck et al., 2003) demonstrated cobalt alone or in combination with tungsten carbide particles induced micronucleated binucleates in human peripheral blood mononucleated cells (PMBC) in a concentration dependent manner. Kang et al. (Kang et al., 2005) demonstrated cobalt-induced Hypoxia inducible factor (HIF) stabilization and IRP-1 activation in human lung carcinoma A459 cells grown in iron- free salt-glucose medium (SGM). If iron was added to the medium, HIF stabilization and IRP-1 activation were reversed. Subsequent studies (Hervouet et al., 2008) focused on the increased formation of ROS and stabilization of HIF-alpha subsequent to cobalt induced decreases mitochondrial oxidative phosphorylation in clear cell renal carcinoma cells. These investigators also noted HIF stimulated increases in ROS formation and mitochondrial manganese superoxide dismutase content. Global gene expression studies (Malard et al., 2007) using human A549 lung cells identified 85 genes

which were either up or down regulated in response to soluble cobalt treatment. These investigators reported that 29 of these genes representing basic cellular functions were evaluated by RT-PCR. And the expression profiles of 6 of these were evaluated by quantitative RT-PCR in a time-dependent manner with confirmation by Western blots. A number of these genes were regarded as putative cobalt carrier proteins, tumor suppressor proteins or transcription factors and genes linked to the stress protein response. The investigators also indentified 9 genes which code for secreted proteins that could serve as possible future biomarkers. The results of these studies are consistent with ROS induction of the stress protein response and alterations of a number of proteins responsible for regulating cellular proliferation. Studies by Witkiewicz and Bal (Witkiewicz-Kucharczyk and Bal 2005) reported damage to zinc finger proteins in DNA repair proteins and suggested that the resultant inhibition of DNA capability may play a role in development of a subsequent carcinogenic response. In addition, recent studies by Li et al. (Li et al., 2009) demonstrated both positive and negative cobalt induced alterations of histone methylation patterns in human lung A549 cells and bronchial epithelial (Beas-2B) cells. These investigators noted the potentially important role of cobalt –induced epigenetic alterations in homeostatic histone methylation patterns in mediating gene expression patterns and the carcinogenic response.

Cobalt with tungsten carbide

Lombaert et al. (Lombaert et al., 2004) studied the apoptotic potential of WC-Co dust, WC and metallic cobalt in human peripheral blood mononucleated cells (PMBC) incubated in vitro with different concentrations of these materials for up to 24 hours. Apoptosis was assessed by Annexin-V staining, flow cytometry (FACS) and ELISA analysis o f DNA fragmentation. Both WC and metallic cobalt particles induced apoptosis and the WC-Co particles appeared to show additivity with respect to this parameter. Interestingly, apoptosis induced by WC particles appeared to be mediated by caspase-9 while that induced by metallic cobalt was mediate by both caspase-8 and caspase-9. The investigators suggest that the apoptosis from WC is due to effects on monocytes while that of metallic cobalt on both monocytes and lymphocytes. WC-Co effects are the result of an additive combination. Subsequent studies by Lombaert et al. (Lombaert et al., 2008) examined the in vitro effects of WC-Co particles on human PMBC gene expression patterns at a 24 hour time point. They observed that the apoptotic, and stress protein pathways were the most markedly up-regulated while the immune response pathways were the most strongly down- regulated in the PMBC. For WC-Co treated monocytes, the nucleosome/chromosome pathways were most up-regulated while the immune response pathways were also most strongly down -regulated. Mateuca et al. (Mateuca et al., 2005) examined the influence of DNA repair enzyme genetic polymorphisms in lymphocytes of workers exposed to cobalt. These investigators found that the incidence of micronucleated mononucleates (MNMC) was elevated in WC-Co exposed workers with the hOGG1(326) genotype base excision enzyme. Multivariate analyses which controlled for a number of potential confounders demonstrated that MNC and comet assay tail DNA were also modified by genetic polymorphisms. In the exposed and total worker populations studied, MNMC frequencies were elevated in those carrying the hOGG1 genotype and XRCC3 double strand break repair enzyme. These data indicate the need for including genotyping in evaluations of workers exposed to these dusts to elucidate those most at risk. The role of glutathione and cysteine SH –group oxidation by WC-Co dust induced ROS formation was studied by Fenoglio et al. (Fenoglio et al., 2008). They reported dust

concentration- dependent generation of thiyl radicals at particle surface sites. It was suggested that this process, in combination with depletion of cellular anti-oxidant defenses, would further exacerbate cellular oxidative damage caused by the WC-Co particle formation of ROS.

Research needs and recommendations

It was noted that there is a proposed study, which is pending a funding decision, to do a cohort (n>10,000) and nested case-control study based at 18 manufacturing sites in the United States, UK, Austria, Germany, Sweden and England. This study is expected to take 4 to 5 years to complete. If it is possible, consideration should be given to this new study incorporating the determination of an appropriate biomarker for exposure. It is recommended that the possibility of updating the French and Swedish studies be explored if they are able to provide sufficient extra data on lung cancer risks, adjusted for potential confounding factors, before the proposed international study. Additional research is also needed to further understand the genetic factors which regulate cellular protective systems in order to better protect sensitive human sub-populations exposed to cobalt with tungsten carbide.

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