Cobalt–Tungsten Carbide: Powders and Hard Metals

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Co/WC, WC/Co

Carcinogenicity

Cobalt–tungsten carbide powders and hard metals are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Epidemiological studies provide evidence for the carcinogenicity of cobalt–tungsten carbide powders and hard metals based on (1) consistent findings of excess lung-cancer mortality among cobalt–tungsten carbide hard-metal manufacturing workers across studies, (2) higher risks among individuals with higher exposure levels, and (3) positive exposure-response relationships that cannot be explained by confounding with tobacco smoking. However, the epidemiological data are limited, because there are few studies of independent populations.

The published epidemiological literature consists of mortality studies of two independent multi-plant cohorts of cobalt–tungsten carbide hard-metal manufacturing workers, one in France (Moulin *et al.* 1998) and one in Sweden (Hogstedt and Alexandersson 1990), and cohort studies of two individual factories included in the French multi-plant cohort (Lasfargues *et al.* 1994, Wild *et al.* 2000). The French multi-plant cohort included all 10 cobalt–tungsten carbide manufacturing plants in France; in addition, a nested case-control study of lung cancer was conducted within this cohort. The nested case-control study is most informative for evaluating cancer risk, because it used a semi-quantitative exposure scale to evaluate exposure-response relationships and considered potential confounding by exposure to tobacco smoking and other known or suspected occupational carcinogens. The cohort study of the largest French factory shares these advantages; however, because the workers were included in the multi-plant study, it does not provide independent evidence for carcinogenicity. In these two studies, four metrics of exposure were evaluated: (1) exposure level, which was the highest exposure score experienced during an individual's work history (on a scale of 0 to 9), (2) duration of exposure at a level of 2 or higher, (3) unweighted cumulative dose, which assigned the same level to occasional and full-time exposure, thus favoring peak exposure, and (4) frequency-weighted cumulative dose, which weighted exposure level by the frequency of exposure, thus reducing the effect of occasional exposure. The Swedish study, although limited in size, provides supporting information for an independent population.

Excess lung-cancer mortality (of approximately 30%) was found in both multi-plant cohort studies (Hogstedt and Alexandersson 1990, Moulin *et al.* 1998); risk estimates were significantly higher among individuals with higher measures of exposure or longer time since first exposure (latency). In the nested case-control study (Moulin *et al.* 1998), lung cancer risk was significantly higher (odds ratio [OR] = 1.93, 95% CI = 1.03 to 3.62, 35 exposed cases) among workers exposed to cobalt–tungsten carbide (exposure level ≥ 2) than among workers with little or no exposure (exposure level < 2). In exposure-response analyses using workers in the lowest exposure category as the comparison group, lung-cancer risk was significantly higher (by up to fourfold) for workers in the highest categories of both measures of cumulative dose, and an elevated risk of borderline statistical significance was found for workers in the highest exposure-level category. Positive exposure-response relationships were observed for all four measures of exposure: duration (P_{trend} = 0.03), unweighted cumulative dose (P_{trend} = 0.01), frequency-weighted cumulative dose (P_{trend} = 0.08), and exposure level (P_{trend} = 0.08). Adjustment for tobacco smoking or exposure to known or suspected carcinogens did not change the results. The Swedish study had limited ability to evaluate exposure-response relationships because of small numbers of exposed workers with lung cancer. Nevertheless, the risk of lung cancer mortality was significantly increased for workers with exposure duration of over 10 years and latency of over 20 years (standardized mortality ratio [SMR] = 2.78, 95% CI = 1.11 to 5.72, 7 exposed cases). Analyses restricted to workers with at least 10 years' exposure or at least 20 years' latency found somewhat higher SMRs for "high-exposed" than "low-exposed" workers (Hogstedt and Alexandersson 1990).

Excess risks of lung-cancer mortality were also found in studies of the two individual French factories. Wild *et al.* (2000) reported significantly elevated SMRs (by approximately twofold) for lung cancer among all male workers and among male workers ever employed in presintering workshops or with exposure levels of at least 2. The highest SMRs were observed for male workers in the highest exposure categories of all four exposure metrics (level, duration, and both measures of cumulative dose), although the trends were not statistically significant, and the risk estimates were imprecise. In the study by Lasfargues *et al.* (1994), the entire cohort had a significantly increased risk of lung cancer, and the risk was highest among workers in the highest exposure-level category. Although small, this study provides supporting evidence that the findings for the French industry-wide cohort were not due solely to the results for the large factory studied by Wild *et al.*

Both the French multi-plant cohort study (Moulin *et al.* 1988) and the larger study of an individual French factory (Wild *et al.* 2000) found higher risks of lung cancer for exposure to cobalt–tungsten carbide before sintering than after sintering (see Production). The authors stated that exposure was highest during presintering processes; however, there is no evidence of toxicological differences between presintered and sintered materials, and both materials release similar amounts of cobalt ions (see Studies on Mechanisms of Carcinogenesis).

It is unlikely that the excess risks of lung cancer found in the French studies were due to confounding by tobacco smoking or co-exposure to other known carcinogens. In the multi-plant study, the smoking-adjusted odds ratio for cobalt–tungsten carbide exposure (OR = 2.6, 95% CI = 1.16 to 5.82) was similar to the unadjusted risk (OR = 2.29, 95% CI = 1.08 to 4.88). Neither study found increased risks of smoking-related diseases, such as chronic bronchitis and emphysema, and adjustment for smoking or exposure to other occupational carcinogens did not change the findings in the exposure-response analyses (Moulin *et al.* 1988, Wild *et al.* 2000). Neither the Swedish multi-plant study (Hogstedt and Alexandersson 1990) nor the small French cohort study (Lasfargues *et al.* 1994) adjusted for smoking; however, surveys of smoking habits among a subset of workers found smoking rates similar to those in the general population. Overall, the studies are limited by the lack of quantitative exposure assessment and potential confounding; however, exposure misclassification would most likely reduce the likelihood of detecting a true effect.

Studies on Mechanisms of Carcinogenesis

The findings from epidemiological studies are supported by studies on mechanisms of carcinogenesis. Although the mechanism(s) by

which by cobalt–tungsten carbide causes cancer have not been fully elucidated, it has been shown that (1) cobalt–tungsten carbide releases cobalt ions, (2) cobalt ions affect biochemical pathways related to carcinogenicity, (3) cobalt compounds are carcinogenic in experimental animals, (4) cobalt–tungsten carbide increases the production of reactive oxygen species (ROS) and causes greater cytotoxic, toxic, and genotoxic effects than does cobalt alone, (5) cobalt–tungsten carbide causes key events related to carcinogenesis, including genotoxicity, cytotoxicity, inflammation, and apoptosis (programmed cell death), and (6) the oxidative stress response resulting from increased ROS production may play a role in these key events and may also interfere with cells' ability to repair damage caused by cobalt–tungsten carbide. The combination of the effects from cobalt ions and the oxidative stress response from ROS production provide plausible modes of action for the carcinogenicity of cobalt–tungsten carbide.

Studies in biological fluids, *in vitro* systems, experimental animals, and humans have demonstrated that cobalt is rapidly solubilized from cobalt–tungsten carbide. Cobalt dissolution rates were similar for presintered and sintered cobalt–tungsten carbide incubated in various artificial biological fluids (Stopford *et al.* 2003). Tungsten is not rapidly solubilized from cobalt–tungsten carbide, but can be phagocytized by macrophages (Lombaert *et al.* 2004). Cobalt was also released from hard-metal dust incubated with plasma and lung tissue (Edel *et al.* 1990). In experimental animals administered cobalt–tungsten carbide by intratracheal administration, cobalt was solubilized rapidly, cleared from the lung, distributed in the body, and excreted in the urine (Lison 1996). Rats exposed intratracheally to cobalt–tungsten carbide had more cobalt in the urine than did rats administered cobalt alone, suggesting that tungsten carbide increases the bioavailability of cobalt (Lasfargues *et al.* 1992). Several biomonitoring studies detected elevated levels of cobalt in the urine, lungs, and other tissues of workers exposed to cobalt–tungsten carbide hard metals (Rizzato *et al.* 1986, Nicolaou *et al.* 1987, Gallorini *et al.* 1994, Sabbioni *et al.* 1994b, Scansetti *et al.* 1994, 1998, Linnainmaa and Kiilunen 1997, Goldoni *et al.* 2004).

Soluble cobalt compounds are genotoxic and carcinogenic in experimental animals. Cobalt sulfate is listed as *reasonably anticipated to be a human carcinogen* in the Report on Carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals. Specifically, inhalation exposure to cobalt sulfate in rodents caused lung tumors (adenoma or carcinoma) in mice and rats and adrenal-gland tumors (pheochromocytoma) in female rats (Bucher *et al.* 1999). Cobalt ions produce ROS, which cause oxidative DNA damage and act on a number of cancer-related molecular targets. Cobalt ions disrupt cell-signaling pathways (Murata *et al.* 1999), inhibit DNA repair (Hartwig 2000, Hartwig *et al.* 2002), regulate genes involved in the response to hypoxia (Beyersmann 2002), replace or mimic essential divalent metal ions, thus altering cellular reactions (Nackerdien *et al.* 1991, Beyersmann and Hartwig 1992, Kawanishi *et al.* 1994, Lloyd *et al.* 1998), and interfere with mechanisms involved in cell-cycle control and modulation of apoptosis (DeBoeck *et al.* 2003b,c).

Numerous *in vitro* studies (reviewed in NTP 2009) and *in vivo* studies (Huaux *et al.* 1995, Lasfargues *et al.* 1995) have shown greater cytotoxic effects (measured primarily by lactate dehydrogenase release) for cobalt–tungsten carbide than for either cobalt powder or tungsten carbide alone. The mixture's greater *in vitro* toxicity to macrophages is not fully explained by greater bioavailability of cobalt (Lison and Lauwerys 1992, 1994). Respirable samples collected at various stages of the hard-metal manufacturing process (including powders for pressing, presintered materials, and powders from grinding of sintered materials) caused cytotoxicity and pathological changes in the lungs of rats after intratracheal injection (Adamis *et al.* 1997). In addition, cobalt–tungsten carbide causes a type of respiratory toxicity ("hard-metal disease") that is not observed with exposure to cobalt alone. Hard-metal disease is characterized by a giant-cell interstitial pneumonia that can develop into lung fibrosis (Lison 1996, Lison *et al.* 1996).

There is some evidence that the greater toxicity of cobalt–tungsten carbide may result from a physicochemical reaction that takes place at the interface between certain carbides and cobalt particles (Lison and Lauwerys 1992). The structural features of the two particles may help to explain the effects. Cobalt metal can reduce ambient oxygen, but only at a low rate of reaction, because of the particles' surface characteristics. Tungsten carbide is inert and does not react with oxygen but is a good electron conductor. When cobalt and tungsten carbide particles are associated, the cobalt electrons are transferred to the carbide surface, allowing increased oxygen reduction and thus increased production of ROS. Biochemical studies on the production of ROS have shown that cobalt's capacity to generate hydroxyl radicals is greatly increased by association with tungsten carbide. Formation of the ROS results directly from the interaction of cobalt with tungsten carbide or indirectly from the cobalt ions generated from the Fenton-like reaction of the cobalt metal with the carbide (Lison and Lauwerys 1993, Lison *et al.* 1995). In oxygen-radical-generating systems, post-sintered powders sampled from final machining (grinding) of cobalt–tungsten carbide products produced higher levels of ROS than did pre-sintered samples of cobalt and tungsten carbide separately or as mixtures (Stefaniak *et al.* 2010).

Metal-induced generation of ROS in cellular test systems leads to oxidative stress as a result of increased free radicals and insufficient antioxidative defense. Protective mechanisms include cellular antioxidant systems, the stress-protein response, and the involvement of DNA excision and repair enzymes (Kasten *et al.* 1997, Shi *et al.* 2004, Lombaert *et al.* 2008). Fenoglio *et al.* (2008) studied oxidation of the antioxidant glutathione and cysteine sulfhydryl groups by cobalt–tungsten carbide dust–induced ROS and reported dust-concentration-dependent generation of thiyl radicals at particle surface sites. Depletion of cellular antioxidant defenses could further exacerbate cellular oxidative damage caused by ROS generated by cobalt–tungsten carbide particles.

Regulation of gene expression, including apoptotic, stress-protein, and immune-response pathways, also can be affected by ROS. Lombaert *et al.* (2008) evaluated the effects of cobalt–tungsten carbide exposure *in vitro* on patterns of gene expression in human peripheral-blood mononucleated cells and reported statistically significant up-regulation of apoptosis and stress or defense response pathways and down-regulation of immune-response pathways.

Apoptosis has been associated with exposure to a number of known carcinogens (arsenic, cadmium, chromium, nickel, and beryllium) and possible carcinogens (cobalt and lead). Cobalt chloride has been shown to induce apoptosis through formation of ROS in both human alveolar macrophages and a rat pheochromocytoma cell line (PC12); co-administration of antioxidants suppressed ROS production and restored cell viability (Zou *et al.* 2001, Araya *et al.* 2002). Cobalt–tungsten carbide, tungsten carbide, and cobalt ions induced apoptosis in human lymphocytes; the effect of the mixture was significantly greater than that of tungsten carbide or cobalt alone (Lombaert *et al.* 2004).

Cobalt–tungsten carbide is genotoxic *in vitro* and causes mutations in the lungs of rats exposed *in vivo.* Its genotoxicity (clastogenic effects) may be caused by increased ROS production from the interaction between cobalt and tungsten carbide, from ionic cobalt, or from both. In addition, cobalt ions inhibit DNA repair, which may also contribute to cobalt–tungsten carbide's genotoxic effects.

Specifically, cobalt–tungsten carbide caused DNA strand breaks in mouse 3T3 fibroblasts and human peripheral-blood lymphocytes (Anard *et al.* 1997) and micronucleus formation in human peripheral-blood lymphocytes (Van Goethem *et al.* 1997, De Boeck *et al.* 2003c). In these studies, cobalt–tungsten carbide was more genotoxic than cobalt alone. In rats exposed by intratracheal instillation, cobalt–tungsten carbide caused DNA damage and micronucleus formation in the lung (type II pneumocytes) (De Boeck *et al.* 2003a). No increase in DNA damage or micronucleus formation was observed in rat peripheral-blood lymphocytes; however, it is unclear whether circulating lymphocytes are a good reporter for monitoring genotoxic effects from inhaled particles. In humans, neither DNA damage nor micronucleus formation was increased in lymphocytes of cobalt–tungsten carbide hard-metal workers, compared with unexposed workers; however, this study was limited by small sample size (De Boeck *et al.* 2000). Multiple regression analyses (Mateuca *et al.* 2005) indicated that both end points were associated with an interaction between tobacco smoking and exposure, and that micronucleus formation was associated with smoking, working in a cobalt–tungsten carbide plant, and having variant forms of genes coding for DNA repair enzymes (X-ray repair cross-complementing group 3 and 8-oxoguanine DNA glycosylase).

In addition, although the pathogenesis of hard-metal disease is not fully understood, it may involve differences in the susceptibility (genetic and/or health-related) of affected individuals to the toxic effects of increased ROS production due to cobalt–tungsten carbide exposure. Further, the mechanisms for fibrosing alveolitis and lung cancer in hard-metal workers may be related, conceivably involving oxidative damage and/or inflammatory events (IARC 2006).

Cancer Studies in Experimental Animals

No studies in experimental animals were identified that evaluated the relationship between cancer and exposure specifically to cobalt–tungsten carbide powders or hard metals.

Properties

This listing includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide. Powders containing both cobalt and tungsten carbide may result from combination of these materials during manufacture of hard metals, and dusts containing both materials may result from production, finishing, or maintenance (e.g., sharpening or grinding) of cobalt–tungsten carbide hard-metal products. Cobalt–tungsten carbide hard metals are composites of tungsten carbide particles (either alone or in combination with smaller amounts of other carbides) with a metallic cobalt powder as a binder, pressed into a compact, solid form at high temperatures by a process known as "sintering." Cobalt–tungsten carbide hard metals are commonly referred to as "cemented carbides" in the United States, but the term "sintered carbide" also may be used, and some sources refer to cobalt–tungsten carbide products simply as "tungsten carbides" (Brookes 2002).

The physical properties of cobalt–tungsten carbide hard metals vary with the relative proportions of cobalt, tungsten carbide, and other carbides, but they have common properties of extreme hardness, abrasion resistance, and toughness. Tungsten carbide is hard (able to resist cutting, abrasion, penetration, bending, and stretching) but brittle; cobalt is soft but tough (able to withstand great strain without tearing or breaking). The composition of commercial-grade cobalt–tungsten carbide hard metals can vary greatly; it generally ranges from 50% to 97% tungsten carbide (along with other metallic carbides such as titanium carbide or tantalum carbide) and from 3% to 16% cobalt, with variations in grain size and additives. The proportion of cobalt as the binding metal in the composite hard metal depends on the intended use (Azom 2002). Cobalt–tungsten carbide hard metals for various uses have Vickers hardness values (a measure of the resistance of a substance to indentation by a diamond penetrator of special profile) typically ranging from 1250 to 1900 (Brookes 1998).

The crystalline structure of cobalt–tungsten carbide includes the structures individually of cobalt, which can exist as either hexagonal or cubic crystals, and tungsten carbide, which consists primarily of W_2C, WC, and possibly other carbides (Upadhyaya 1998b). The phase diagram for the combination of cobalt and tungsten carbide is extremely complex, as tungsten can form a solid solution in cobalt, and cobalt can form carbides with carbon; the overall relationship varies with the concentrations of the major components and the temperature.

Mixtures of cobalt and tungsten carbide are more active than the individual components in adsorption of water vapor (with respect to both the amount adsorbed and the interaction energy) and in the catalytic decomposition of hydrogen peroxide (Zanetti and Fubini 1997). Physical and chemical properties of tungsten carbide and cobalt are listed in the following table.

Property	Cobalt	Tungsten carbide
Molecular or atomic weight	58.9	195.9
Density	8.92	15.6
Melting point	1,495°C	2,785°C
Boiling point	2,927°C	6,000°C
Vapor pressure	1 Pa at 1,517°C (0.0075 mmHg)	NR

Source: HSDB 2010. NR = not reported.

Use

About 70% of cobalt–tungsten carbide hard-metal production is used for cutting tools and 30% for wear-resistant materials, primarily for tools for mining and grinding operations (Santhanam 2003). Hard-metal grades for machining are assigned International Organization for Standardization (ISO) codes beginning with "P" for machining of steel, "M" for multiple purposes, including machining of steel, nickel-based superalloys, and ductile cast iron, and "K" for cutting of gray cast iron, nonferrous metals, and nonmetallic materials.

Production

Cobalt–tungsten carbide hard metals were developed in Germany during and after World War I and marketed commercially by a German company in 1927 as Widia, which consisted of tungsten carbide with 6% cobalt as binder (Brookes 1998, Upadhyaya 1998a). Cobalt–tungsten carbide hard-metal manufacturing processes vary somewhat, but all involve production of cobalt and tungsten carbide powders, which are mixed, pressed into a compact, solid form, and sintered by heating to about 1,500°C. The manufacturing process consists of three steps: Step 1, producing the cobalt and tungsten carbide powders; Step 2, mixing, drying, pressing, presintering, shaping the presintered hard metal, and sintering; and Step 3, finishing the sintered products, which includes grinding and sharpening.

Worldwide use of cemented carbides has increased steadily over the years, from about 10 tons in 1930 to 30,000 tons per year in the early 2000s (Azom 2002). In 2004, estimated U.S. production of hard-metal products totaled 5,527 metric tons (6,080 tons) (Hsu 2004). The U.S. Geological Survey (USGS 2008a,b) estimated that 792 metric tons (873 tons) of cobalt (9.3% of total U.S. cobalt consumption) and 6,610 metric tons (7,286 tons) of tungsten (56% of total U.S. tungsten consumption) was used in the production of cemented carbides in the United States in 2007. In 2008, 127 U.S. and Canadian compa-

nies were identified that produced or supplied cobalt–tungsten carbide and materials made from cobalt–tungsten carbide (ThomasNet 2008), and the Cemented Carbide Producers Association had 22 U.S. members and partner members (CCPA 2008). In 2007, the United States imported about 1.6 million kilograms (1,800 tons) and exported about 1.3 million kilograms (1,400 tons) of tungsten carbide (USITC 2008); no data specific to U.S. imports or exports of cobalt–tungsten carbide were found.

Exposure

The major source of exposure to cobalt–tungsten carbide powders and hard metals is occupational. However, people who live in the vicinity of hard-metal production or maintenance facilities could be exposed to cobalt–tungsten carbide hard-metal dusts. Although no exposure levels for the general population were found, some studies provided data on possible environmental contamination from the manufacture or maintenance of hard-metal products. Soil sampled from the rear of a cemented carbide tool-grinding plant contained cobalt at concentrations of up to 12,780 mg/kg (Abraham and Hunt 1995). The concentrations of tungsten and cobalt in airborne particulates in Fallon, Nevada, and four nearby towns were characterized by Sheppard *et al.* (2006), who found higher levels of tungsten (0.1 to 40.9 ng/m^3) and cobalt (0.02 to 0.16 ng/m^3) in Fallon than in the other towns. The authors suggested that a hard-metal facility located in Fallon could be a candidate source for airborne exposure to the metals, a suggestion that has been disputed (see NTP 2009).

Sources of occupational exposure to cobalt–tungsten carbide during the manufacture of hard metals include the processes of mixing, drying, pressing, presintering, shaping, and sintering (parts of Step 2, as described under Production) and the processes of grinding and sharpening sintered products (parts of Step 3, as described under Production). Exposure to cobalt–tungsten carbide hard metals can also occur from other miscellaneous manufacturing operations, during processing of hard-metal scrap for recycling, and during end use and maintenance of hard-metal tools. Particle size (and hence respirable fraction), morphology, and concentrations of airborne dusts and bulk dusts were found to differ among production areas (Stefaniak *et al.* 2007). For cobalt-containing particles, the minimum mass median aerodynamic diameter (MMAD) was 6 µm (for dry grinding), and the maximum MMAD was over 18 µm (for scrap reclamation and pressing operations); the MMAD for powder mixing was around 10 µm, which is generally considered the maximum diameter for respirable particles in humans. Inhalable, thoracic, and respirable particles were found in all work areas of three facilities that together carried out the cobalt–tungsten carbide manufacturing process, with the highest levels reported for the powder-mixing area (Stefaniak *et al.* 2009). Cobalt and tungsten have been detected in workers' urine, blood, hair, toenails, and bronchoalveolar lavage fluid, and through open lung and transbronchial biopsy (NTP 2009).

Step 2 processes, particularly powder-processing operations, generally are associated with the highest airborne exposures; several studies reported cobalt concentrations approaching or exceeding 5,000 µg/m^3 (NTP 2009). A maximum mean cobalt air concentration of 32,740 µg/m^3 (range = 44 to 438,000 µg/m^3) was reported during weighing and mixing operations in a U.S. manufacturing facility (Sprince *et al*. 1984). An Italian study reported a mean tungsten air concentration of 26 µg/m^3 (Sabbioni *et al*. 1994a), and a German study reported a maximum single measurement of 254 µg/m^3 (Kraus *et al*. 2001). Among workers involved in Step 2 manufacturing processes, cobalt was detected in the urine (at up to 2,100 µg/L), blood or serum (at up to 32 µg/L), and hair (at up to 25.8 ppm), and tungsten was detected in urine (at up to 169 µg/L).

Cobalt air concentrations reported for Step 3 processes (including tool finishing, grinding, and reconditioning operations) have generally been lower than those for Step 2, but have exceeded 1,000 µg/m^3 in some studies (NTP 2009). For Step 3 processes, a maximum mean cobalt air concentration of 1,292 µg/m^3 and a maximum single measurement of 2,440 µg/m^3 were reported, both for dry-grinding operations. For tungsten in air, a maximum mean concentration of 5,160 µg/m^3 and a maximum single measurement of 12,800 µg/m^3 were reported. Among workers involved specifically in Step 3 processes, cobalt was detected in urine (at up to 730 µg/L), blood (at up to 39 µg/L), and hair (at up to 9.11 ppm). Tungsten also was detected in urine (at up to 1,000 µg/L) and blood (at up to 60 µg/L).

A few studies reported on exposure for jobs outside of the cobalt–tungsten carbide production process. McDermott (1971) reported airborne cobalt concentrations during packing operations (10 to 250 µg/m^3), equipment cleaning (40 to 820 µg/m^3), and miscellaneous operations (10 to 6,700 µg/m^3), but the nature of these operations was not defined further. Maintenance activities (including housekeeping) were reported by Scansetti *et al.* (1985) to result in airborne cobalt concentrations exceeding 50 µg/m^3, and Kraus *et al.* (2001) reported urinary levels associated with maintenance activities ranging from 1.3 to 4.7 µg/L for cobalt and 1.5 to 5.3 µg/L for tungsten.

Information on exposure from the end use of hard-metal tools is limited; however, exposure appears to be minimal. Pellet *et al.* (1984) reported cobalt air concentrations of 180 to 193 µg/m^3 and a mean urinary cobalt concentration of 11.7 µg/L associated with use of hard metal; however, no additional information was provided for these data. No other information was found that directly demonstrated exposure to cobalt–tungsten carbide powders and hard metals by end users of products containing the material. The Washington State Department of Labor, in a Hazard Alert issued in March 1995, stated that there was no evidence of substantial exposure to cobalt during the use of tools containing tungsten carbide or other hard metals (WSDLI 1995).

Several studies found significant correlations between cobalt concentrations in air and in workers' blood or urine (Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994b). Urinary cobalt levels for hard-metal workers have been reported to increase through the workday (Torra *et al.* 2005) and workweek (Lison *et al*. 1994, Scansetti *et al*. 1998, Torra *et al.* 2005). In one study, urinary cobalt concentrations were significantly higher ($P < 0.005$) at the end of a shift than at the beginning of the shift, with significant increases "day in and day out" during the workweek (Torra *et al.* 2005).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Water Act

Tungsten and cobalt discharge limits are imposed for numerous processes during the production of tungsten or cobalt at secondary tungsten and cobalt facilities processing tungsten or tungsten carbide scrap raw materials.

Discharge limits for tungsten are imposed for numerous processes during the production of tungsten at primary tungsten facilities.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limits (PEL) (8-h TWA) = 0.1 mg/m^3 for cobalt metal, dust, and fume (as Co); = 5 mg/m^3 for insoluble tungsten compounds (as W).

Short-term exposure limits (STEL) = 10 mg/m^3 for insoluble tungsten compounds (as W).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m^3 for cobalt and inorganic cobalt compounds; = 5 mg/m^3 for tungsten metal and insoluble compounds.

Threshold limit value – short-term exposure limit (TLV-STEL) = 10 mg/m^3 for tungsten metal and insoluble compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 15 µg/L for cobalt in urine; = 1 µg/L for cobalt in blood.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m^3 for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m^3 for cobalt metal dust and fume (as Co); = 5 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m^3 for cobalt metal dust and fume (as Co).

Short-term exposure limit (STEL) = 10 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

References

Abraham JL, Hunt A. 1995. Environmental contamination by cobalt in the vicinity of a cemented tungsten carbide tool grinding plant. *Environ Res* 69(1): 67-74.

Adamis Z, Tatrai E, Honma K, Karpati J, Ungvary G. 1997. A study on lung toxicity of respirable hard metal dusts in rats. *Ann Occup Hyg* 41(5): 515-526.

Anard D, Kirsch-Volders M, Elhajouji A, Belpaeme K, Lison D. 1997. *In vitro* genotoxic effects of hard metal particles assessed by alkaline single cell gel and elution assays. *Carcinogenesis* 18(1): 177-184.

Angerer J, Heinrich R. 1988. Chapter 20: Cobalt. In *Handbook on Toxicity of Inorganic Compounds*. Seiler HG, Sigel H, eds. New York: Marcel Dekker. pp. 251-264.

Araya J, Maruyama M, Inoue A, Fujita T, Kawahara J, Sassa K, *et al.* 2002. Inhibition of proteasome activity is involved in cobalt-induced apoptosis of human alveolar macrophages. *Am J Physiol Lung Cell Mol Physiol* 283(4): L849-L858.

Azom. 2002. *Tungsten Carbide — An Overview.* The A to Z of Materials. http://www.azom.com/Details.asp?ArticleID=1203.

Beyersmann D, Hartwig A. 1992. The genetic toxicology of cobalt. *Toxicol Appl Pharmacol* 115(1): 137-145.

Beyersmann D. 2002. Effects of carcinogenic metals on gene expression. *Toxicol Lett* 127(1-3): 63-68.

Brookes K. 2002. Through the looking glass—the rather odd world of hardmetals. *Metal Powder Report* 57(5): 28-29.

Brookes KJA. 1998. *Hardmetals and Other Hard Materials,* 3rd ed. East Barnet, Hertfordshire, England: International Carbide Data. 220 pp.

Bucher JR, Hailey JR, Roycroft JR, Haseman JK, Sills RC, Grumbein SL, Mellick PW, Chou BJ. 1999. Inhalation toxicity and carcinogenicity studies of cobalt sulfate. *Toxicol Sci* 49(1): 56-67.

CCPA. 2008. *Cemented Carbide Producers Association – Members*. Cemented Carbide Producers Association. http://www.ccpa.org/pages/members.html. Last accessed: 10/6/08.

De Boeck M, Lardau S, Buchet JP, Kirsch-Volders M, Lison D. 2000. Absence of significant genotoxicity in lymphocytes and urine from workers exposed to moderate levels of cobalt-containing dust: a cross-sectional study. *Environ Mol Mutagen* 36(2): 151-160.

De Boeck M, Hoet P, Lombaert N, Nemery B, Kirsch-Volders M, Lison D. 2003a. *In vivo* genotoxicity of hard metal dust: induction of micronuclei in rat type II epithelial lung cells. *Carcinogenesis* 24(11): 1793-1800.

De Boeck M, Kirsch-Volders M, Lison D. 2003b. Cobalt and antimony: genotoxicity and carcinogenicity. *Mutat Res* 533(1-2): 135-152.

De Boeck M, Lombaert N, De Backer S, Finsy R, Lison D, Kirsch-Volders M. 2003c. *In vitro* genotoxic effects of different combinations of cobalt and metallic carbide particles. *Mutagenesis* 18(2): 177-186.

De Boeck M, Kirsch-Volders M, Lison D. 2004. Corrigendum to "Cobalt and antimony: genotoxicity and carcinogenicity" [Mutat Res 533 (2003) 135-152]. *Mutat Res* 548(1-2): 127-128.

Edel J, Sabbioni E, Pietra R, Rossi A, Torre M, Rizzato G, Fraioli P. 1990. Trace metal lung disease: *In vitro* interaction of hard metals with human lung and plasma components. *Sci Total Environ* 95: 107-117.

Fenoglio I, Corazzari I, Francia C, Bodoardo S, Fubini B. 2008. The oxidation of glutathione by cobalt/tungsten carbide contributes to hard metal-induced oxidative stress. *Free Radic Res* 42(8): 737-745.

Gallorini M, Edel J, Pietra R, Sabbioni E, Mosconi G. 1994. Cobalt speciation in urine of hard metal workers — a study carried out by nuclear and radioanalytical techniques. *Sci Total Environ* 150(1-3): 153-160.

Goldoni M, Catalani S, De Palma G, Manini P, Acampa O, Corradi M, Bergonzi R, Apostoli P, Mutti A. 2004. Exhaled breath condensate as a suitable matrix to assess lung dose and effects in workers. *Environ Health Perspect* 112(13): 1293-1298.

Hartwig A. 2000. Recent advances in metal carcinogenicity. *Pure Appl Chem* 72(6): 1007-1014.

Hartwig A, Asmuss M, Ehleben I, Herzer U, Kostelac D, Pelzer A, Schwerdtle T, Bürkle A. 2002. Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. *Environ Health Perspect* 110(Suppl 5): 797-799.

Hogstedt C, Alexandersson R. 1990. Dödsorsaker hos Hardmetallarbetare. *Arbete och Hälsa* 21: 1-26.

HSDB. 2010. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on cobalt, elemental; and search on tungsten carbide. Last accessed: 4/15/10.

Hsu WY. 2004. Hsu WY, Kennametal, Inc., Latrobe, PA, letter to Jameson CW, National Toxicology Program, Research Triangle Park, NC, July 16, 2004.

Huaux F, Lasfargues G, Lauwerys R, Lison D. 1995. Lung toxicity of hard metal particles and production of interleukin-1, tumor necrosis factor-alpha, fibronectin, and cystatin-c by lung phagocytes. *Toxicol Appl Pharmacol* 132(1): 53-62.

IARC. 2006. *Cobalt in Hard-metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide,* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 86, Lyon, France: International Agency for Research on Cancer. 330 pp.

Ichikawa Y, Kusaka Y, Goto S. 1985. Biological monitoring of cobalt exposure, based on cobalt concentrations in blood and urine. *Int Arch Occup Environ Health* 55(4): 269-276.

Kasten U, Mullenders LH, Hartwig A. 1997. Cobalt(II) inhibits the incision and the polymerization step of nucleotide excision repair in human fibroblasts. *Mutat Res* 383(1): 81-89.

Kawanishi S, Inoue S, Yamamoto K. 1994. Active oxygen species in DNA damage induced by carcinogenic metal compounds. *Environ Health Perspect* 102(Suppl 3): 17-20.

Kraus T, Schramel P, Schaller KH, Zöbelein P, Weber A, Angerer J. 2001. Exposure assessment in the hard metal manufacturing industry with special regard to tungsten and its compounds. *Occup Environ Med* 58(10): 631-634.

Lasfargues G, Wild P, Moulin JJ, Hammon B, Rosmorduc B, Rondeau du Noyer C, Lavandier M, Moline J. 1994. Lung cancer mortality in a French cohort of hard-metal workers. *Am J Ind Med* 26(5): 585-595.

Lasfargues G, Lardot C, Delos M, Lauwerys R, Lison D. 1995. The delayed lung responses to single and repeated intratracheal administration of pure cobalt and hard metal powder in the rat. *Environ Res* 69(2): 108-121.

Linnainmaa M, Kiilunen M. 1997. Urinary cobalt as a measure of exposure in the wet sharpening of hard metal and stellite blades. *Int Arch Occup Environ Health* 69(3): 193-200.

Lison D. 1996. Human toxicity of cobalt-containing dust and experimental studies on the mechanism of interstitial lung disease (hard metal disease). *Crit Rev Toxicol* 26(6): 585-616.

Lison D, Lauwerys R. 1992. Study of the mechanism responsible for the elective toxicity of tungsten carbide-cobalt powder toward macrophages. *Toxicol Lett* 60(2): 203-210.

Lison D, Lauwerys R. 1993. Evaluation of the role of reactive oxygen species in the interactive toxicity of carbide-cobalt mixtures on macrophages in culture. *Arch Toxicol* 67(5): 347-351.

Lison D, Lauwerys R. 1994. Cobalt bioavailability from hard metal particles: Further evidence that cobalt alone is not responsible for the toxicity of hard metal particles. *Arch Toxicol* 68(8): 528-531.

Lison D, Buchet JP, Swennen B, Molders J, Lauwerys R. 1994. Biological monitoring of workers exposed to cobalt metal, salt, oxides, and hard metal dust. *Occup Environ Med* 51(7): 447-450.

Lison D, Carbonnelle P, Mollo L, Lauwerys R, Fubini B. 1995. Physicochemical mechanism of the interaction between cobalt metal and carbide particles to generate toxic activated oxygen species. *Chem Res Toxicol* 8(4): 600-606.

Lison D, Lauwerys R, Demedts M, Nemery B. 1996. Experimental research into the pathogenesis of cobalt/hard metal lung disease. *Eur Respir J* 9(5): 1024-1028.

Lloyd DR, Carmichael PL, Phillips DH. 1998. Comparison of the formation of 8-hydroxy-2′-deoxyguanosine and single- and double-strand breaks in DNA mediated by Fenton reactions. *Chem Res Toxicol* 11(5): 420-427.

Lombaert N, De Boeck M, Ecordier I, Undari E, Lison D, Irsch-Volders M. 2004. Evaluation of the apoptogenic potential of hard metal dust (WC-Co), tungsten carbide, and metallic cobalt. *Toxicol Lett* 154: 23-34.

Lombaert N, Lison D, Van Hummelen P, Kirsch-Volders M. 2008. *In vitro* expression of hard metal dust (WC-Co) -responsive genes in human peripheral blood mononucleated cells. *Toxicol Appl Pharmacol* 227: 299-312.

Mateuca R, Aka PV, De Boeck M, Hauspie R, Kirsch-Volders M, Lison D. 2005. Influence of *hOGG1*, *XRCC1* and *XRCC3* genotypes on biomarkers of genotoxicity in workers exposed to cobalt or hard metal dusts. *Toxicol Lett* 156(2): 277-288.

McDermott FT. 1971. Dust in the cemented carbide industry. *Am Ind Hyg Assoc J* 32(3): 188-193.

Moulin JJ, Wild P, Romazini S, Lasfargues G, Peltier A, Bozec C, Deguerry P, Pellet F, Perdrix A. 1998. Lung cancer risk in hard-metal workers. *Am J Epidemiol* 148(3): 241-248.

Murata M, Gong P, Suzuki K, Koizumi S. 1999. Differential metal response and regulation of human heavy metal-inducible genes. *J Cell Physiol* 180(1): 105-113.

Nackerdien Z, Kasprzak KS, Rao G, Halliwell B, Dizdaroglu M. 1991. Nickel(II)- and cobalt(II)-dependent damage by hydrogen peroxide to the DNA bases in isolated human chromatin. *Cancer Res* 51(21): 5837-5842.

Nicolaou G, Pietra R, Sabbioni E, Mosconi G, Cassina G, Seghizzi P. 1987. Multielement determination of metals in biological specimens of hard metal workers: a study carried out by neutron activation analysis. *J Trace Elem Electrolytes Health Dis* 1(2): 73-77.

NTP. 2009. *Report on Carcinogens Background Document for Cobalt-Tungsten Carbide Powders and Hard Metals*. National Toxicology Program. http://ntp.niehs.nih.gov/files/Hard_MetalsBD-FINAL_(SCG-17Mar09).pdf .

Pellet F, Perdrix A, Vincent M, Mallion JM. 1984. Biological levels of urinary cobalt. *Arch Mal Prof* 45: 81-85 (as cited in Angerer and Heinrich 1988).

Pulido MD, Parrish AR. 2003. Metal-induced apoptosis: mechanisms. *Mutat Res* 533(1-2): 227-241.

Rizzato G, Lo Cicero S, Barberis M, Torre M, Pietra R, Sabbioni E. 1986. Trace of metal exposure in hard metal lung disease. *Chest* 90(1): 101-106.

Sabbioni E, Minoia C, Pietra R, Mosconi G, Forni A, Scansetti G. 1994a. Metal determinations in biological specimens of diseased and non-diseased hard metal workers. *Sci Total Environ* 150(1-3): 41-54.

Sabbioni E, Mosconi G, Minoia C, Seghizzi P. 1994b. The European Congress on cobalt and hard metal disease. Conclusions, highlights and need of future studies. *Sci Total Environ* 150(1-3): 263-270.

Santhanam AT. 2003. Carbides, cemented. In *Kirk-Othmer Encyclopedia of Chemical Technology,* vol. 4. Online edition. New York: John Wiley & Sons. pp. 655-674.

Scansetti G, Lamon S, Talarico S, Botta GC, Spinelli P, Sulotto F, Fantoni F. 1985. Urinary cobalt as a measure of exposure in the hard metal industry. *Int Arch Occup Environ Health* 57(1): 19-26.

Scansetti G, Botta GC, Spinelli P, Reviglione L, Ponzetti C. 1994. Absorption and excretion of cobalt in the hard metal industry. *Sci Total Environ* 150(1-3): 141-144.

Scansetti G, Maina G, Botta GC, Bambace P, Spinelli P. 1998. Exposure to cobalt and nickel in the hard-metal production industry. *Int Arch Occup Environ Health* 71(1): 60-63.

Sheppard PR, Ridenour G, Speakman RJ, Witten ML. 2006. Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: possible implications for the childhood leukemia cluster. *Appl Geochem* 21: 152-165.

Shi H, Hudson LG, Liu KJ. 2004. Oxidative stress and apoptosis in metal ion-induced carcinogenesis. *Free Radic Biol Med* 37(5): 582-593.

Sprince NL, Chamberlin RI, Hales CA, Weber AL, Kazemi H. 1984. Respiratory disease in tungsten carbide production workers. *Chest* 86(4): 549-557.

Stefaniak AB, Day GA, Harvey CJ, Leonard SS, Schwegler-Berry DE, Chipera SJ, Sahakian NM, Chisholm WP. 2007. Characteristics of dusts encountered during the production of cemented tungsten carbides. *Ind Health* 45:793-803.

Stefaniak AB, Virji MA, Day GA. 2009. Characterization of exposures among cemented tungsten carbide workers. Part I: Size-fractionated exposures to airborne cobalt and tungsten particles. *J Expo Sci Environ Epidem* 19(5): 475-491.

Stefaniak AB, Harvey CJ, Bukowski VC, Leonard SS. 2010. Comparison of free radical generation by pre- and post-sintered cemented carbide particles. *J Occup Environ Hyg* 7: 23-34.

Stopford W, Turner J, Cappellini D, Brock T. 2003. Bioaccessibility testing of cobalt compounds. *J Environ Monit* 5(4): 675-680.

Sueker JK. 2006. Comment on "Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: Possible implications for the childhood leukemia cluster," by Sheppard PR, Ridenour G, Speakman RJ, and Witten ML. *Appl Geochem* 21: 1083-1085.

ThomasNet. 2008. *Metals: Carbide*. Thomas Publishing. http://www.thomasnet.com/products/tungsten-carbide-89540207-1.html. Last accessed: 9/24/08.

Torra M, Fernández J, Rodamilans M, Navarro AM, Corbella J. 2005. Biological monitoring of cobalt exposure: results in a non-exposed population and on workers of a hard metal manufacture. *Trace Elem Electroly* 22(3): 174-177.

Upadhyaya GS. 1998a. Classification and applications of cemented carbides. In *Cemented Tungsten Carbides. Production, Properties, and Testing*. Westwood, NJ: Noyes Publications. pp. 288-293.

Upadhyaya GS. 1998b. Crystal structure and phase equilibria. In *Cemented Tungsten Carbides. Production, Properties, and Testing*. Westwood, NJ: Noyes Publications. pp. 7-54.

USGS. 2008a. *Mineral Industry Surveys: Cobalt in October, November and December 2007*. Reston, VA: U.S. Geological Survey.

USGS. 2008b. *Mineral Industry Surveys: Tungsten in January 2008*. Reston, VA: U.S. Geological Survey.

USITC. 2008. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 284990. Last accessed: 9/24/08.

Van Goethem F, Lison D, Kirsch-Volders M. 1997. Comparative evaluation of the in vitro micronucleus test and the alkaline single cell gel electrophoresis assay for the detection of DNA damaging agents: genotoxic effects of cobalt powder, tungsten carbide and cobalt-tungsten carbide. *Mutat Res* 392(1-2): 31-43.

Wild P, Perdrix A, Romazini S, Moulin JJ, Pellet F. 2000. Lung cancer mortality in a site producing hard metals. *Occup Environ Med* 57(8): 568-573.

WSDLI. 1995. *Hard-Metal Workers Face Risks from Cobalt, Cadmium*. WISHA Hazard Alert. State of Washington Department of Labor and Industries. http://www.lni.wa.gov/Safety/Basics/HazAlerts/951a.asp.

Zanetti G, Fubini B. 1997. Surface interaction between metallic cobalt and tungsten carbide particles as a primary cause of hard metal lung disease. *J Mater Chem* 7(8): 1647-1654.

Zou W, Yan M, Xu W, Huo H, Sun L, Zheng Z, Liu X. 2001. Cobalt chloride induces PC12 cells apoptosis through reactive oxygen species and accompanied by AP-1 activation. *J Neurosci Res* 64(6): 646-653.