# Report on Carcinogens
# Background Document for

# Cobalt–Tungsten Carbide: Powders and Hard Metals

March 2009

National Toxicology Program
U.S. Department of Health and Human Services
Public Health Service
Research Triangle Park, NC 27709

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# FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are known to be human carcinogens or are reasonably be anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services (HHS), has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP), which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed or (3) removing a substance already listed in the RoC are reviewed by a multi-step, scientific review process with multiple opportunities for public comment. The scientific peer review groups evaluate and make independent recommendations for each substance according to specific RoC listing criteria. This draft Background Document was prepared to assist in the review of 'cobalt–tungsten carbide: powders and hard metals.' The scientific information used to prepare Sections 3 through 5 of this document must come from publicly available, peer-reviewed sources. Information in Sections 1 and 2, including chemical and physical properties, analytical methods, production, use, and occurrence may come from published and/or unpublished sources. The NTP will provide a reference for all published and unpublished sources used in this document. For each study cited in the background document from the peer-reviewed literature, information on funding sources (if available) and the authors' affiliations will be provided in the reference section. Any interpretive conclusions, comments, or statistical calculations made by the authors of this draft document that are not contained in the original citation are identified in brackets [ ]. This draft document will be peer reviewed in a public forum by an *ad hoc* expert panel of scientists from the public and private sectors with relevant expertise and knowledge selected by the NTP in accordance with the Federal Advisory Committee Act and HHS guidelines and regulations. This document will be finalized based on the peer-review recommendations of the expert panel and public comments received for this draft document.

A detailed description of the RoC nomination review process and a list of all substances under consideration for listing in or delisting from the RoC can be obtained by accessing the 12th RoC at http://ntp.niehs.nih.gov/go/9732. The most recent RoC, the 11th Edition (2004), is available at http://ntp.niehs.nih.gov/go/19914.

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## PEER-REVIEW

The draft background document on Cobalt–Tungsten Carbide: Powders and Hard Metals was peer reviewed by the Report on Carcinogens (RoC) expert panel for Cobalt–Tungsten Carbide: Powders and Hard Metals. The panel met in a public forum at the Sheraton Chapel Hill Hotel, Chapel Hill, NC on December 9–10, 2008. Members of the expert panel are as follows:

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## Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

## U.S. Department of Health and Human Services

## National Toxicology Program

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are as follows:

***Known To Be Human Carcinogen:***

**There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.**

***Reasonably Anticipated To Be Human Carcinogen:***

**There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,**

**or**

**there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,**

**or**

**there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.**

**Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.**

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

# Executive Summary

## Introduction

This candidate substance includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide (hereafter referred to as "hard metals"). Hard metals are also referred to as cemented (or sintered) carbides, or simply as tungsten carbides. Cobalt–tungsten carbide hard metals are composites of tungsten carbide particles (either tungsten carbide alone or in combination with smaller amounts of other carbides) with 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 have properties of extreme hardness, abrasion resistance, and toughness and are used primarily in cutting tools and wear-resistant machine parts.

In 2003, the International Agency for Research on Cancer (IARC) reviewed the carcinogenicity of metallic cobalt particles, with or without tungsten carbide, and cobalt sulfate and other soluble cobalt (II) salts. IARC concluded that there was limited evidence in humans for the carcinogenicity of cobalt metal with tungsten carbide, and the overall evaluation was that cobalt metal with tungsten carbide was *probably carcinogenic to humans* (Group 2A) (IARC 2006).

## Human Exposure

Hard metals are used primarily in cutting tools, to machine tempered steel, in rock drilling bits, and in a variety of tools. They are produced by preparing tungsten carbide particles from tungsten metal or tungsten oxide and carbon, adding a mixture of powdered cobalt metal and other compounds to produce powders of cobalt–tungsten carbide, which are then pressed, shaped, sintered, and finished as hard-metal products. Total U.S. domestic production of hard-metal products was estimated at 5,527 metric tons [6,080 tons] in 2004, and the USGS estimated that 6,610 metric tons [7,286 tons] of tungsten and 792 metric tons [873 tons] of cobalt were used in the production of cemented carbides in the United States in 2007.

Workers potentially are exposed to respirable dusts at many points during the manufacturing process, and dermal exposures also have been demonstrated. Exposure can be assessed by measuring ambient air concentrations of cobalt or tungsten or by biological monitoring, including measurements of cobalt or tungsten in urine, blood, tissues, or exhaled air. Exposure generally is highest among workers handling hard metal in powder form before or during the sintering process (Step 2). Exposure also can occur during the grinding or sharpening of hard-metal blades (Step 3) and from other processes. At facilities that use hard metals, exposure is generally highest for individuals who are involved in the maintenance, sharpening, and grinding of tools. Historically, exposure levels from production have decreased over time, possibly as a result of improved industrial hygiene in hard-metal producing factories.

The potential exists for general-population exposures to cobalt–tungsten carbide hard metals or to powders containing cobalt and tungsten carbide for persons living near facilities that manufacture or process cobalt-tungsten carbide hard metals or hard-metal products. There is one OSHA regulation specific to cemented tungsten carbide (a synonym for hard metals), although there are numerous other regulations for cobalt and tungsten metals and compounds. Similarly, there is one guideline for cemented tungsten carbide and numerous guidelines for cobalt and tungsten metals and compounds.

**Human Cancer Studies**

Workers producing powders or hard metals consisting of cobalt–tungsten carbide are exposed to either presintered or sintered hard-metal particles. Four cohort studies (although not mutually independent) were identified that evaluated exposure to hard metals and cancer mortality. These studies included (1) a cohort study of Swedish workers at three hard-metals facilities (Hogstedt and Alexandersson 1990), (2) a small cohort of French hard-metal manufacturing workers (Lasfargues *et al.* 1994), (3) a multi-plant cohort study of workers at 10 hard-metal producing factories in France, which also included a nested case-control analysis (Moulin *et al.* 1998), and (4) a cohort study of the largest factory of the multi-plant French study (Wild *et al.* 2000). The multi-plant study also included workers studied by Lasfargues *et al.* All of the studies attempted to evaluate exposure-response relationships, although the exposure assessments by Hogstedt and Alexandersson and Lasfargues *et al.* were crude. Both Wild *et al.* and Moulin *et al.* attempted to control for smoking and/or other occupational exposure.

All four studies reported an increased lung cancer risk, with significantly increased lung cancer mortality either in the whole cohort or among workers with higher or longer exposure, or longer latency. Hogstedt and Alexandersson found significant excess lung cancer mortality in a subgroup of long-latency, long-exposure–duration workers, and Lasfargues *et al.* found a five-fold significantly elevated SMR in their high-exposure group. Moulin *et al.* (1998) found an overall increase in lung cancer mortality of borderline statistical significance and a significantly increased risk for exposure levels higher than level 2 (on a scale of 0 to 9) compared with the lowest level. In the nested case-control study, the risk of lung cancer increased significantly with duration of exposure ($P = 0.03$) and cumulative dose (unweighted) ($P = 0.01$) and increased non-significantly with exposure level ($P = 0.08$) and cumulative dose (frequency weighted) ($P = 0.08$). Adjustment for smoking or known or suspected carcinogens did not change the ORs. Wild *et al.* (2000) found significantly elevated lung cancer SMRs among all workers and workers ever employed in pre-sintering workshops, and among the highest exposure category (exposure score, unweighted cumulative exposure, weighted cumulative exposure) to hard-metal dusts. In models controlling for smoking and exposure to any "IARC carcinogen" (PAHs, silica, nickel compounds, chromium compounds, or cobalt without tungsten), the test for trend was of borderline significance for exposure duration and was not significant for exposure level or cumulative dose. In analyses that evaluated exposure to unsintered hard metals, a significantly increased trend for duration of exposure was found in models that controlled for smoking and exposure to any "IARC carcinogen." No increased risk for exposure to sintered metals was found in this model.

Hogstedt and Alexandersson was the only study to evaluate risks for tumors sites other than lung in more detail, such as evaluation of risks by exposure groups, exposure duration, and individual factory. They reported a significant excess risk for leukemia among workers employed at one of the factories and exposed for less than 5 years, but not among longer exposed workers. A non-significant excess of leukemia was found among the small cohort study of French workers (Lasfargues *et al.*), but not among the larger studies (Moulin *et al.*, Wild e*t al.*). Non-significant excesses of cancer of the esophagus (Lasfargues *et al*., Moulin *et al.*, Wild *et al.*), upper gastrointestinal tract (Moulin *et al.*, Wild *et al*.), and pleura (Moulin *et al.,* Wild *et al.*) were found in the overlapping French studies.

**Studies in Experimental Animals**

No studies of the carcinogenicity of hard metals in experimental animals were identified.

**Absorption, Distribution, Metabolism, and Excretion**

Humans are exposed to cobalt–tungsten carbide hard-metal particles through inhalation and dermal contact. Hard-metal particles of respirable size are potentially deposited throughout the respiratory tract, including in the alveoli. Studies in humans and animals have demonstrated that when hard-metal particles are deposited in the lung, cobalt metal is rapidly solubilized, cleared from the lung, distributed in the body, and excreted in urine, whereas tungsten carbide particles persist longer in lung tissue. Rats administered cobalt–tungsten carbide intratracheally excreted significantly greater amounts of cobalt in the urine as compared with rats administered cobalt metal, suggesting that cobalt has a greater bioavailability when combined with tungsten carbide. In hard-metal workers, cobalt has been detected in urine, whole blood, pubic hair, and toenails, and tungsten has been detected in urine, feces, pubic hair, and toenails.

**Toxicity**

Cobalt–tungsten carbide hard-metal dust has been shown to be more toxic than pure cobalt or tungsten carbide in the lungs of rats and *in vitro* in rodent cells (mouse peritoneal macrophages and rat alveolar macrophages) and human cells (type II pneumocytes). Differences in cellular cobalt uptake alone cannot account for the greater toxicity of cobalt–tungsten carbide hard-metal particles than pure cobalt. Occupational inhalation exposure to hard-metal dust is associated in some workers with the occurrence of hard-metal disease, a giant-cell interstitial pneumonia that can develop into pulmonary fibrosis, with a potentially fatal outcome. Other toxic effects reported in hard-metal workers include contact dermatitis, occupational asthma, and memory loss.

**Mechanistic and Genotoxicity Data**

[Toxicity and genotoxicity appear to be mediated both by solubilized cobalt ions and through a surface chemistry reaction between cobalt and tungsten carbide that occurs at the particulate level.] Several *in vitro* and *in vivo* studies have demonstrated that the interaction between cobalt metal and tungsten carbide particles and molecular oxygen

produces reactive oxygen species, which are involved directly or indirectly (e.g., via a lipoperoxidation process) in the genotoxicity of cobalt–tungsten carbide hard metals.

Genotoxicity studies have demonstrated that cobalt–tungsten carbide hard metals cause DNA damage and micronucleus formation in human peripheral blood lymphocytes *in vitro* and in type II pneumocytes (but not peripheral blood lymphocytes) of rats exposed *in vivo*. A study evaluating the genotoxic effects of occupational exposure to cobalt–tungsten carbide hard-metal particles did not find increased DNA damage or micronucleus formation in blood lymphocytes of exposed workers. Cobalt–tungsten carbide hard-metal particles caused significantly more (approximately threefold increased) DNA breaks and micronuclei in cultured human lymphocytes than cobalt particles alone.

Cobalt–tungsten carbide hard-metal carcinogenicity might also be mediated via the release of cobalt ions. Cobalt ions can be solubilized from cobalt–tungsten carbide particles in biological media, which could generate high levels of the metal in target cells. Genotoxic effects of cobalt ions, which include DNA strand breaks in the comet assay and micronucleus formation, might result, at least in part, from inhibition of DNA repair mechanisms. Cobalt ions also have been shown to modulate apoptosis, regulate genes involved in the response to hypoxia, and replace or mimic essential divalent metal ions in proteins regulating cell-cycle control and DNA repair, thus altering cellular reactions. For example, cobalt ions could inhibit dioxygenase enzymes, such as the prolyl hydroxylase responsible for signaling degradation of hypoxia-inducible factor-1$\alpha$ by displacing bound iron at the active site of the enzymes. Several cobalt compounds (cobalt sulfate, cobalt chloride, and cobalt naphthenate) and cobalt metal cause tumors in experimental animals. Cobalt sulfate is listed in the *Report on Carcinogens, Eleventh Edition* as *reasonably anticipated to be a human carcinogen*.

Tungsten carbide particles have been shown to be phagocytosed by macrophages, and the combination of metallic tungsten with cobalt and nickel has been reported to cause tumors at the implantation site in rats, and the same combination was genotoxic *in vitro*. In addition, tungsten added to the drinking water of rats treated with *N*-nitroso-*N*-methylurea (NMU) was reported to promote the formation of mammary tumors. Neither tungsten metal nor tungsten carbide has been reviewed by the National Toxicology Program for possible listing in the *Report on Carcinogens* or by IARC.

# Abbreviations

8-OHdG: 8-hydroxydeoxyguanosine

ACGIH: American Conference of Governmental Industrial Hygienists

BAL: bronchoalveolar lavage

BALF: bronchoalveolar lavage fluid

BEI: biological exposure indices

BHT: butylated hydroxytoluene

b.w.: body weight

CCPA: Cemented Carbide Producers Association

CHO: Chinese hamster ovary

CI: confidence interval

Co: cobalt

$Cr_3C_2$: chromium carbide

DHHS: Department of Health and Human Services

Fpg: formamido-pyrimidine DNA glycosylase

HIP: hot isostatic pressing

HLA: human leukocyte antigen

HOS: human osteosarcoma

HV: hardness Vickers

ICD-8: International Classification of Diseases- $8^{th}$ edition

ICD-9: International Classification of Diseases- 9th edition

IL-1: interleukin-1

i.p. : intraperitoneal

IARC: International Agency for Research on Cancer

ISO: International Organization for Standardization

$K_{ow}$: octanol-water partition coefficient

$K_{sp}$: solubility product constant

LDH: lactate dehydrogenase

$Mo_2C$: molybdenum carbide

mol wt: molecular weight

NAG: *N*-acetyl-β-D-glucosaminidase

NbC: niobium carbide

NMU: *N*-nitroso-*N*-methylurea

NTP: National Toxicology Program

OR: odds ratio

Pa: pascal; the SI unit of pressure

PAHs: polycyclic aromatic hydrocarbons

ppb: parts per billion

PBMC: peripheral blood mononucleated cells

PDGF: platelet-derived growth factor

ppm: parts per million

RoC: Report on Carcinogens

ROS: reactive oxygen species

RTECS: Registry of Toxic Effects of Chemical Substances

s.c.: subcutaneous

SCE: sister chromatid exchange

SHE: Syrian hamster embryo

SMR: standardized mortality ratio

TaC: tantalum carbide

Ta(Nb)C: tantalum niobium carbide

TiC: titanium carbide

TLV: threshold limit value

TNFα: tumor necrosis factor-α

TWA: time-weighted average

UDS: unscheduled DNA synthesis

W: tungsten

WC: tungsten carbide

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# 1 Introduction

This candidate substance includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide (hereafter referred to as "hard metals"). Powders containing both cobalt and tungsten carbide may result from combining 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 hard metal products. Hard metals of cobalt–tungsten carbide are composites of tungsten carbide particles (either tungsten carbide 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." 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).

Cobalt–tungsten carbide hard metals have properties of extreme hardness, abrasion resistance, and toughness and are used primarily in cutting tools and wear-resistant machine parts. Exposure to hard metals occurs in the production of hard metals, during the grinding of hard-metal blades, and through the use of the products. However, exposure is expected to be limited from the normal end-use of the cobalt–tungsten carbide tools because of their resistance to wear. 'Cobalt–tungsten carbide: powders and hard metals' were nominated for possible listing in the *Report on Carcinogens* (RoC) based on human epidemiological studies that reported an excess of mortality from lung cancer in hard-metal manufacturing workers.

An extensive review of cobalt metal with tungsten carbide was conducted by the International Agency for Research on Cancer (IARC) in 2003. The working group reviewed the carcinogenicity of metallic cobalt particles, with or without tungsten carbide, and cobalt sulfate and other soluble cobalt (II) salts. IARC concluded that there was limited evidence in humans for the carcinogenicity of cobalt metal with tungsten carbide, inadequate evidence in humans for the carcinogenicity of cobalt metal without tungsten carbide, and sufficient evidence in experimental animals for the carcinogenicity of cobalt sulfate and cobalt metal powder, and the results of the meeting were published in 2006 (IARC 2006). The overall evaluation was that cobalt metal with tungsten carbide was *probably carcinogenic to humans* (Group 2A); cobalt sulfate is listed in the *Report on Carcinogens, Eleventh Edition* as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. Tungsten carbide alone has not been reviewed by either the National Toxicology Program or IARC.

## 1.1 Identification and physical-chemical properties

"Hard metal" is a generic term for composite materials produced by powder metallurgy and combining a carbide with a metallic binder. A composite is a material formed by combining two or more materials present as distinct phases, so as to take advantage of desirable properties of each component. In the case of hard metals, hard ceramic particles (carbides) are present within a ductile-metal matrix material. Most commonly, hard metals are composites of tungsten carbide (WC, including tungsten carbide alone or in

combination with small amounts of other carbides) and metallic cobalt (Kirk-Othmer 1997), and this nomination is specific for these types of hard metals and their powders and dusts. Cobalt–tungsten carbide hard metals have properties of extreme hardness, abrasion resistance, and toughness.

Cobalt–tungsten carbide hard metals were developed in Germany during and after World War I and were first marketed commercially by a German company in 1927 as *Widia* (wie Diamant or diamond-like), which consisted of tungsten carbide with 6% cobalt as a binder (Brookes 1998, Upadhyaya 1998). Hard-metal production in Germany was highly secretive, particularly during World War II. Following the end of that war, British Intelligence published a report detailing German production techniques, control methods, and research projects for hard metal, and this report was used by many hard-metal manufacturers outside of Germany in the years following the war. Many developments in the production of hard metals since World War II have taken place in the United States, Austria, Sweden, Japan, and other countries. The secrecy that surrounded hard-metal production techniques during and after World War II contributed to a continuing problem of a lack of a single, uniform standard based on compositions and properties of hard metals. As discussed further below, the existing coding systems are based on applications for the products, and, as a result, many hundreds of potential compositions of cobalt, tungsten carbide, and other metals and their carbides are manufactured by different producers. As a result of these widely varying compositions, no uniform set of physical-chemical properties can be defined for the mixture of cobalt and tungsten carbide in hard metals.

Cobalt–tungsten carbide hard metals have undergone many improvements, through changes in manufacturing methods and materials (Kirk-Othmer 1997). The process materials are fine powders, and hard-metal manufacture uses powder metallurgy techniques. Tungsten carbide and cobalt form a solid through the process of sintering: a mixture of tungsten carbide particles and powdered cobalt is heated to between 1,350°C and 1,550°C, and the solid is formed through diffusion of cobalt, which may occur even at temperatures below its melting point (1,495°C) (Kriz 2004).

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). Cobalt–tungsten carbide hard metals combine the hardness of tungsten carbide with the toughness of cobalt. Their physical properties vary with the relative proportions of cobalt, tungsten carbide, and other carbides and depend on the following factors (Brookes 1998):

- compositions and relative proportions of the phases (e.g., metal and carbide);
- size, shape, and distribution of carbide particles;
- degree of intersolubility of carbides;
- excess or deficiency of carbon;
- variations in composition and structure caused by diffusion, precipitation, or segregation;

- production methods generally, but especially milling, carburizing (production of tungsten carbide from tungsten and carbon), and sintering methods, and the choice of raw materials;
- post-sintering treatments, such as hot isostatic pressing; and
- coatings or diffusion layers applied or developed after initial sintering.

In general, the hardness and abrasion resistance of hard metals increase with decreasing size of the tungsten carbide particles and decreasing cobalt content (provided that enough cobalt is present to ensure complete liquid-phase sintering) (Brookes 1998).

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; see Table 1-1) 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 is a function of the use of the material. For cutting tools, when the major use is for coarse machining, the binding-metal content is higher, to provide increased toughness, while for finish machining, the binding-metal content is lower (Azom 2004).

There is no uniform system for assuring the composition of hard metals (MPR 2002); several classification systems are accepted worldwide (Kirk-Othmer 1997, Upadhyaya 1998). One classification system for use as highly wear-resistant machine parts (wear parts) is based on International Organization for Standardization (ISO) application codes. However, a classification system for hard metals used for cutting tools has not been successful, because of the importance of other physical properties (Kirk-Othmer 1997). Table 1-1 shows representative compositions and physical properties of hard metals for use as wear parts by ISO application code. The ISO application codes are for guidance only; the coding is at the manufacturer's discretion (Brookes 1998).

**Table 1-1. Physical properties of cobalt–tungsten carbide hard-metal grades for machining by ISO application code**

| ISO code[a] | Composition (%) | | | | Density ($g/cm^3$) | Hardness[b] (HV) |
|---|---|---|---|---|---|---|
| | WC | TiC | Ta(Nb)C | Co | | |
| P01 | 50 | 35 | 7 | 6 | 8.5 | 1900 |
| P05 | 78 | 16 | – | 6 | 11.4 | 1820 |
| P10 | 69 | 15 | 8 | 8 | 11.5 | 1740 |
| P15 | 78 | 12 | 3 | 7 | 11.7 | 1660 |
| P20 | 79 | 8 | 5 | 8 | 12.1 | 1580 |
| P25 | 82 | 6 | 4 | 8 | 12.9 | 1530 |
| P30 | 84 | 5 | 2 | 9 | 13.3 | 1490 |
| P40 | 85 | 5 | – | 10 | 13.4 | 1420 |
| P50 | 78 | 3 | 3 | 16 | 13.1 | 1250 |
| M10 | 85 | 5 | 4 | 6 | 13.4 | 1590 |
| M20 | 82 | 5 | 5 | 8 | 13.3 | 1540 |
| M30 | 86 | 4 | – | 10 | 13.6 | 1440 |
| M40 | 84 | 4 | 2 | 10 | 14 | 1380 |
| K01 | 97 | – | – | 3 | 15.2 | 1850 |
| K05 | 95 | – | 1 | 4 | 15 | 1780 |
| K10 | 92 | – | 2 | 6 | 14.9 | 1730 |
| K20 | 94 | – | – | 6 | 14.8 | 1650 |
| K30 | 91 | – | – | 9 | 14.4 | 1400 |
| K40 | 89 | – | – | 11 | 14.1 | 1320 |

Source: Brookes 1998.
[a]P = used to machine steel; M = used for multiple purposes, including machining of steels, nickel-based superalloys, and ductile cast irons; K = used to cut gray cast iron, non-ferrous metals, and non-metallics.
[b]HV = Vickers hardness (measures the resistance to indentation by a diamond penetrator of special profile).

## 1.2 Physical-chemical properties of tungsten carbide and cobalt

The physical and chemical properties of tungsten carbide and cobalt are summarized in Table 1-2. Zanetti and Fubini (1997) studied the surface interaction of cobalt and tungsten carbide particles and determined that the mixture of cobalt and tungsten carbide is more active than the individual components in terms of the adsorption of water vapor, in both the adsorbed amount and interaction energy, and in the catalytic decomposition of hydrogen peroxide. Tungsten carbide has a hardness of approximately 9 on the Mohs scale (slightly less hard than diamond) (O'Brien 1996), while cobalt has a hardness of 5 (also on the Mohs scale) (EnvironmentalChemistry.com 2005, FurnXpert 2005).

**Table 1-2. Physical and chemical properties of tungsten carbide and cobalt**

| Property | Tungsten carbide | Cobalt |
|---|---|---|
| molecular weight | 195.9 | 58.9 |
| color | gray | gray |
| physical state | hexagonal crystals | hexagonal or cubic metal |
| melting point (°C) | 2,785 | 1,495 |
| boiling point (°C) | 6,000 | 2,927 |
| density | 15.6 | 8.92 |
| solubility<br>water<br>nitric acid, hydrogen fluoride | <br>insoluble<br>soluble | <br>NA<br>soluble (dilute nitric acid) |
| octanol-water partition coefficient (log $K_{ow}$) | NA | NA |
| vapor pressure | NA | 1 Pa (1,517°C) |
| vapor density | NA | NA |
| Henry's law constant | NA | NA |

Sources: HSDB 2006a, 2006b.
NA = not available.

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# 2 Human Exposure

Exposure to cobalt–tungsten carbide hard metals, powders, and dust can occur in hard-metal producing plants, and in the grinding and sharpening of tools after use. Even though hard-metal tools are widely used, the potential for exposure to end-users (other than those involved in the maintenance, sharpening, and grinding of the tools) is likely to be quite small since the hardness of the cobalt–tungsten carbide material results in only small amounts of wear during normal use. Environmental exposure might occur from living near a cobalt–tungsten carbide hard-metal manufacturing or processing facility.

This section discusses use (Section 2.1), production (Section 2.2), hard-metal manufacturing and occupational exposure (Section 2.3), biological indicators of exposure (Section 2.4), environmental levels and general population exposure (Section 2.5), regulations and guidelines for hard metals (Section 2.6), and an overall summary (Section 2.7). Numerous synonyms are used in the literature for cobalt–tungsten carbide hard metals, including "cemented carbides," "sintered carbides," "tungsten carbide," and the general term "hard metals." In order to provide the most accurate representation of the literature, no attempt was made to standardize the term used for hard metals, but rather, the terms that were used in the referenced documents are used here.

## 2.1 Use

Since the 1920s, cobalt–tungsten carbide hard metal has been used as the main material in cutting tools in lathes and other industrial machines to machine materials such as tempered steel. It is also used in rock drilling bits, masonry drills, woodcutting tools, studs for golf and other specialized shoes (Brookes 1998), and many other products. Approximately 70% of hard-metal production is used for cutting tools and 30% for wear-resistant materials, primarily tools for mining and grinding operations (Kirk-Othmer 1997).

## 2.2 Production

Worldwide use of cemented carbides has increased steadily over the years, from approximately 10 tons in 1930 to approximately 30,000 tons per year in the early 2000s (Azom 2004). From 1990 to 1996, 20 U.S. companies reported estimated production of at least 10 metric tons [11 tons], with an average annual production of 147 metric tons [162 tons] per company (Brookes 1996). [However, many additional producers were identified without any estimates of annual production. Therefore, the actual production level of hard-metal containing cobalt and tungsten carbide was likely much higher.] In a public comment received from Kennametal, Inc. in response to a *Federal Register* notice of May 19, 2004 (FR 2004), Hsu (2004) reported that a USGS estimate from 2004 put the total domestic (U.S.) production of hard-metal products at 5,527 metric tons [6,080 tons]. The United States Geological Survey (USGS 2008a, 2008b) 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] were used in the production of cemented carbides in the United States in 2007.

The Thomas Register (2008) identified 127 U.S. and Canadian companies that produced or supplied cobalt–tungsten carbide and materials made from the compound. In 1996, approximately 1,000 U.S. companies were identified as hard-metal producers or suppliers (Brookes 1996); however, this figure included wholesalers and retailers of finished hard-metal products. The Cemented Carbide Producers Association in the United States has 22 members or partner members (CCPA 2008). In 2007, the United States exported approximately 1.3 million kilograms [1,427 tons] and imported approximately 1.6 million kilograms [1,778 tons] of tungsten carbide (ITA 2008); however, no data were reported specific to cobalt–tungsten carbide.

## 2.3 Hard-metal manufacturing and occupational exposure

It is difficult to estimate the number of people in the United States who may be occupationally exposed to hard metals; however, in a public comment received from Kennametal, Inc. in response to a *Federal Register* notice of May 19, 2004 (FR 2004), Hsu (2004) reported that Kennametal, as the largest U.S. hard-metal manufacturing company (consuming an estimated 70% of the tungsten used for U.S. production of hard-metal products), employed approximately 1,700 people in the manufacture of hard-metal products. The number of employees at the companies manufacturing the remaining 30% of hard-metal products is not known, but as noted above (Section 2.2), over 20 other U.S. companies each manufactured at least 10 metric tons [11 tons] of hard metals in the early 1990s.

This section discusses the general stages associated with the production of hard metals (Section 2.3.1), the chemical and physical characteristics of the hard-metal dusts across the production process (Section 2.3.2), the processes involved in the recycling and recovery of hard metals (Section 2.3.3), occupational exposure for various manufacturing processes (Section 2.3.4), exposure levels associated with Step 2 and other processes (see below for description of Steps 1, 2, and 3) (Section 2.3.5), exposure during finishing of sintered hard-metal products (Step 3) (Section 2.3.6), exposure to end-users (other than grinders or sharpeners) (Section 2.3.7), and non-process specific exposure data for hard-metal production (Section 2.3.8).

### *2.3.1 Manufacturing processes*

Hard-metal manufacturing processes vary somewhat, but all have the same basic elements involving production of cobalt and tungsten carbide powders followed by mixing the powders and pressing into a compact, solid form and heating to a temperature of approximately 1,500°C: a process known as "sintering." The process is illustrated in Figure 2-1 and is divided into the following three steps representing different stages in the manufacturing process: Step 1, producing the cobalt and tungsten carbide powders; Step 2, mixing the powders, drying, pressing, presintering, shaping the presintered hard metal, and sintering; and Step 3, finishing the sintered products.

Many variations exist for the manufacturing process, but generally, in a typical process, the potential for exposure to cobalt–tungsten carbide begins when the sized and defined cobalt and tungsten carbide powders are weighed, mixed, and screened (Step 2 in Figure 2-1). The powder mixtures are then added to vessels containing organic solvents (usually

heptane or similar solvents) and further mixed and milled, and a binder such as paraffin or polyethylene glycol is added. The slurry is dried and then molded into the general shape of the final item by any of a number of processes, such as hydrostatic, isostatic, or mechanical pressing. At this point, the work pieces, held together by paraffin or similar agents, are soft and easily machined. Parts may go directly to machining (e.g., with lathes or milling machines) or may be presintered at 500°C to 800°C before machining. The products are then sintered at high temperature (1,350°C to 1,550°C), which increases diffusion between the binder metal and the carbide, eliminating voids and porosities in the composite material, and removes the paraffin or other temporary binding agent. Sintering is done in vacuum ovens and may be followed by hot isostatic pressing. After sintering, parts may be sandblasted or shotblasted in conjunction with machining, usually in glove boxes or hoods (Step 3 in Figure 2-1). Sintered parts typically are finished by wet- or dry-grinding processes. In some cases, parts are surface-coated with materials such as titanium nitride for increased wear resistance through chemical or physical vapor deposition in a sealed reactor process (Kirk-Othmer 1997, Tucker Jr. 1996).

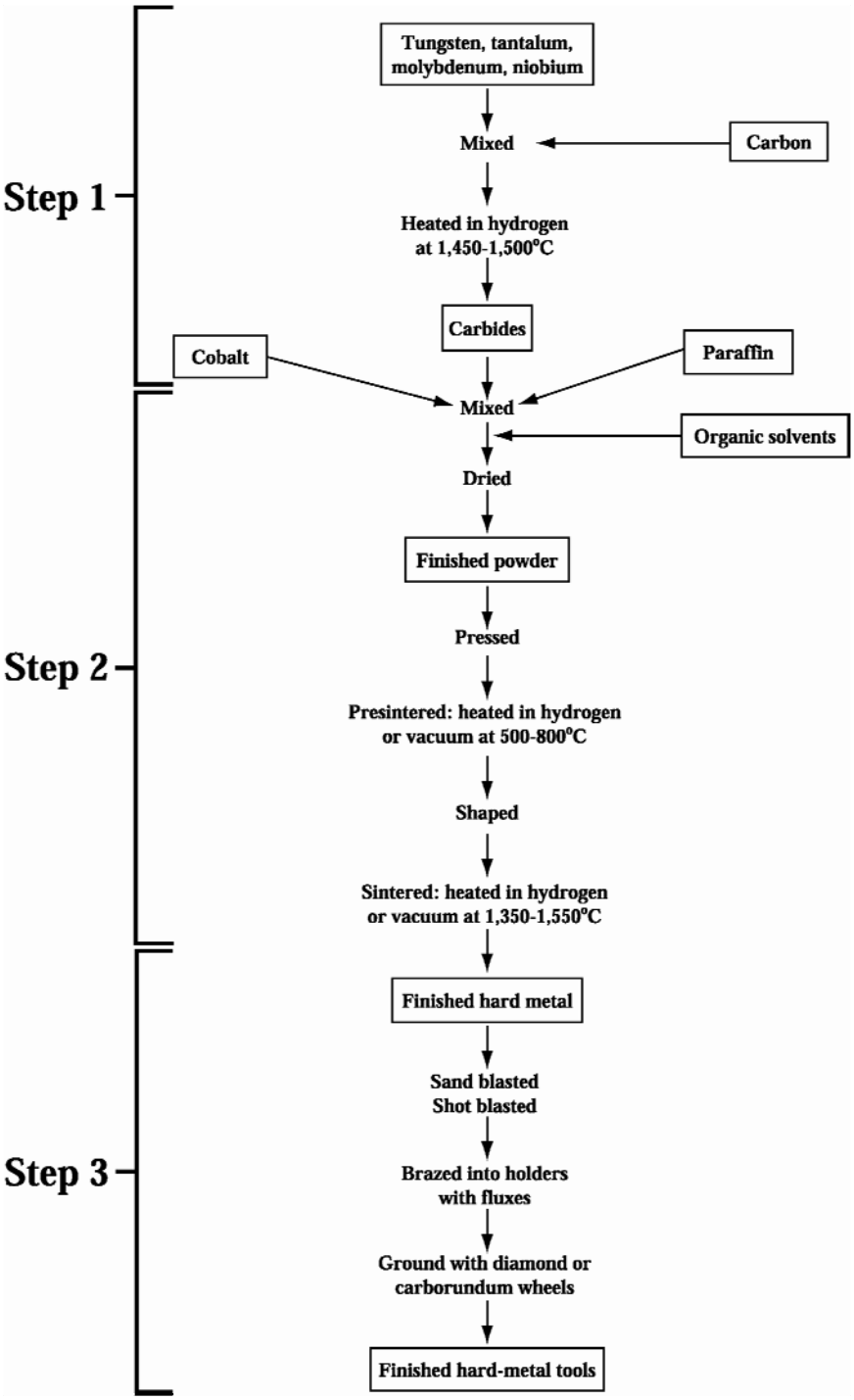


**Figure 2-1. Hard-metal manufacturing process**

Typical steps in the process of manufacturing hard metals from cobalt and tungsten carbide are shown. The portions of the process bracketed on the left and labeled as Step 1, Step 2, and Step 3 are described further in Section 2.3.1 and in Section 3, Human Cancer Studies, in relation to the epidemiologic studies of cancer in the hard-metal manufacturing industry.

Source: Adapted from Kusaka *et al.* 1986b, with permission.

### 2.3.2 Characteristics of hard-metal dusts across the production process

Yamada *et al.* (1987) and Linnainmaa *et al.* (1996) analyzed dusts from different stages and found no difference in particle size or shape. However, Stefaniak *et al.* (2007) noted differences in particle size [and hence respirable fraction], morphology, and concentrations for airborne dusts and bulk dusts from different production areas. Mass median aerodynamic diameter (MMAD) was smallest for grinding operations (2 μm) and largest for scrap reclamation operations (> 18 μm). [Note that scrap reclamation was not part of the operations process for data reported by Yamada *et al.* (1987) and Linnainmaa *et al.* (1996) discussed above.] For cobalt-containing particles, the minimum MMAD was 6 μm (dry grinding) and the maximum MMAD was > 18 μm (both for scrap reclamation and pressing operations); the MMAD was around 10 μm for powder mixing. [In general, particles with a diameter of less than 10 μm are considered respirable.]

Airborne dust concentrations were highest in mixing operations (4,031 $\mu g/m^3$) and lowest in dry-grinding operations (128 $\mu g/m^3$) (Stefaniak *et al.* 2007). It was noted that cobalt concentrations in airborne dust varied by a factor of almost 200, with the lowest concentrations in dry grinding (1 $\mu g/m^3$), and the highest levels in scrap reclamation (192 $\mu g/m^3$). The authors pointed out that the particles were predominantly non-respirable in the operations with the highest concentrations.

Both Stefaniak *et al.* (2007) and Koponen *et al.* (1982) reported that the morphology of particles changes through the production process. These authors reported that in the mixing stage of the production process, tungsten and cobalt were seen as discrete particles; however, in all subsequent stages of production, heterogeneous, multi-constituent particles consisting of cobalt, tungsten, and various additives were seen, and these particles differed from each other based on the stage of production. Koponen *et al.* reported that grinding of hard-metal pieces generated dusts with similar amounts of tungsten and cobalt compared with dusts generated during the mixing of the raw powders. Lichstenstein *et al*. (1975) and Stebbins *et al*. (1992) sampled grinding operations for total and respirable airborne concentrations of cobalt and reported levels exceeding the ACGIH TLV level (20 $\mu g/m^3$.)

### 2.3.3 Hard-metal recycling

Recycled hard-metal scrap is an important source of tungsten and cobalt for industrial processes, including hard-metal production (USGS 2004), and as noted above, the recycling process is a potential source of significant exposure. The recycling processes that are used can be classified as either direct or indirect. In direct recycling, the hard-metal is disaggregated by processes including the coldstream process and the zinc process, and the finer tungsten carbide and cobalt powders that result are ready to use to make new hard metals. The zinc process is considered the most important direct recycling process in the United States for hard-metals recycling (USGS 2005). In indirect processes, the individual components (e.g., tungsten and cobalt) are recovered and purified separately using chemical processes, such as chlorination, nitrate or nitrite-carbonate fusion, and oxidation-sodium hydroxide leaching, with the latter being the most common in the United States (USGS 2004, 2005).

In the United States, in the late 1990s it was estimated that 35% of hard-metal scrap was recycled using chemical processes, 25% using the zinc process, and 5% using other methods: the remaining 35% of scrap was not recycled (USGS 2005). Hard-metal producers will often supply scrap to converters for reuse, and some facilities have their own recycling operations. Some of the recycling operations result in high dust levels (Kirk-Othmer 1997), although Stefaniak *et al.* (2007) reported that the respirable fraction of particles from these processes is generally low.

### *2.3.4 Occupational exposure for various manufacturing processes*

The major source of exposure to hard metals is from occupational exposure, which can occur at almost any stage of hard-metal production. [Note that no combined exposure to cobalt and tungsten carbide would be expected to occur in Step 1.] Sources of exposure can include Step 2 processes from the mixing of the cobalt and tungsten carbide powders through sintering, and Step 3 processes of grinding and sharpening sintered products (see Figure 2-1). Step 2 processes are generally associated with the highest airborne exposures, with levels up to approximately 7,000 μg/m$^3$ for cobalt reported in several studies (see Table 2-3). In comparison, the cobalt levels for the finishing operations in Step 3 did not exceed 1,000 μg/m$^3$ (see Table 2-4). Exposure to cobalt–tungsten carbide hard metals also can occur during processing of hard-metal scrap for recycling and from other miscellaneous operations as well as for operations outside of the direct manufacturing process and during end-use and maintenance of hard-metal tools. [Note that Tables 2-3 and 2-4 briefly summarize the data for exposure, and additional data for the same studies are reported in Appendix B, Tables B-1 and B-2.]

Occupational exposures reported for Step 2 are discussed in Section 2.3.5, those for Step 3 in Section 2.3.6, and exposures that were reported for hard-metal manufacture but were not process specific are reported in Section 2.3.7. The studies by Kraus *et al.* (2001) in Germany and Kumagai *et al.* (1996) in Japan are discussed separately since they reported exposures across a broad range of processes (across Steps 2 and 3), and the levels for the various processes reported in these studies are summarized in Tables 2-1 and 2-2. The highest cobalt air level presented by Kraus *et al.* (343 μg/m$^3$) was based on one personal sample during sintering; however, a level of 1.3 μg/m$^3$ was reported for one stationary sample during sintering. [The relatively low levels of urinary cobalt for workers involved in sintering and the low tungsten air levels during sintering reported in the same study suggest that the high air level based on a single sample might be an anomaly.] Aside from that singular level for sintering, pressing operations and powder processing resulted in the highest air levels for both cobalt and tungsten. Both wet- and dry-grinding operations resulted in relatively low airborne exposure levels for cobalt; however, for tungsten, a low level was seen for wet grinding, but a moderately high level was seen for dry grinding. These airborne tungsten levels, however, were not associated with urinary tungsten levels. The highest tungsten urinary levels for all work categories were found among wet grinders (mean = 70.9 μg/g creatinine), but the mean airborne exposure level of 3.3 μg/m$^3$ for personal monitoring in this work area was the lowest reported for any workshop.

Kumagai *et al*. (1996) similarly found the highest cobalt air levels in powder preparation and press operations, with moderate levels from grinding operations. Kumagai *et al*. also reviewed the components of variance across a variety of job groups within a hard-metal tool manufacturing facility by collecting 935 samples from 275 workers over a period of 5 years. They reported that the within-worker variation ranged from 1.88 to 2.77 geometric standard deviations (GSD) and between-worker variation ranged from 1.00 to 2.31 GSD, demonstrating low day-to-day and between worker variability. [Personal exposures to workplace agents are known to be highly variable and conform to a lognormal distribution. If a large variance exists, then it is less possible to detect significant associations between exposure and disease. However, Kumagai *et al*. found that the GSDs were less than 3.0, showing low variability.]

**Table 2-1. Personal ambient air monitoring[a] and urinary levels for cobalt and tungsten in various workshops in a hard-metal manufacturing plant in Germany**

| Workshop | Cobalt | | Tungsten | |
|---|---|---|---|---|
| | Air (μg/m$^3$), range {N} | Urine (μg/g CR), mean (range) {N} | Air (μg/m$^3$) {N} | Urine (μg/g CR), mean (range) {N} |
| Forming | 0.61–2.82 {5} | 13.5 (0.75–106) {23} | 7.8–97.4 {5} | 10.7 (0.33–33.1) {23} |
| Pressing | 0.87–116 {3} | 5.5 (0.36–35.9) {30} | 5.3–211 {3} | 8.6 (1.5–71.0) {30} |
| Powder processing | 7.9–64.3 {4} | 28.5 (0.75–228) {14} | 177.0–254 {4} | 12.2 (2.6–25.1) {14} |
| Production of tungsten carbide | 0.39 {1} | 2.1 (0.31–5.7) {4} | 19.1 {1} | 42.1 (10.0–60.6) {4} |
| Sintering | 343[b] {1} | 4.1 (0.31–9.6) {6} | 5.9–12.1 {1} | 12.5 (2.1–46.8) {6} |
| Grinding (wet) | 0.20 {1} | 2.2 (0.19–6.0)[c] {5} | 3.3 {1} | 94.4 (10.6–169)[c] {5} |
| Grinding (dry) | 0.48 {1} | | 81.3 {1} | |
| Heavy alloy production | 0.85–1.84 {2} | 1.6 (1.1–2.0) {3} | 50.0–417 {2} | 24.9 (2.6–50.5) {3} |
| Maintenance | NR | 3.0 (1.3–4.7) {2} | NR | 3.4 (1.5–5.3) {2} |

Source: Kraus *et al.* 2001.
CR = creatinine; N = number of samples; NR = not reported.
[a] Personal sampling with 37-mm–diameter filters with a pore size of 0.8 μm.
[b] A single stationary air monitoring sample from the sintering area contained 1.3 μg/m$^3$.
[c] Type of grinding process not specified for urinary results.

**Table 2-2. Cobalt exposure levels for workers in a hard-metal factory in Japan**

| Job Group | No. of workers (N) | Exposure level (μg/m$^3$) Mean (range) |
|---|---|---|
| Powder preparation | | |
| rotation | 15 (60) | 459 (7–6,390) |
| full-time | 2 (12) | 147 (26–378) |
| Press | | |
| rubber | 8 (26) | 339 (48–2,910) |
| steel | 23 (34) | 47 (6–248) |
| Shaping | 67 (179) | 97 (4–1,160) |
| Sintering | 37 (82) | 24 (1–145) |
| Blasting | 3 (7) | 2 (1–4) |
| Electron-discharge machining | 10 (18) | 3 (1–12) |
| Grinding | 191 (517) | 45 (1–482) |

Source: Kumagai *et al.* 1996.
N = number of samples.

Hard-metal coatings can be applied to the surface of tools by the process of detonation coating, which is generally done in sealed booths. Workers may be contaminated with dusts that did not contact the target parts (overspray). These dusts may be re-aerosolized when workers enter the booth after the coating process (Keane *et al.* 2002). [No data were found on exposure levels from these operations, however.]

### *2.3.5 Exposure levels associated with Step 2 and other processes*

Numerous studies have characterized exposure levels (air and biological) across the various stages of hard-metal production, but the processes in Step 1 (see Figure 2-1) are not expected to involve combined exposures to cobalt and tungsten, although cobalt was reported to be detectable in air at a relatively low level (0.39 μg/m$^3$) during production of tungsten carbide in the study by Kraus *et al.* (2001). The exposure data specific to Step 2 of the hard-metal production process is described below, and the various studies are summarized in Table 2-3. Information on exposure during reclamation of scrap hard metal and on exposure to non-production personnel at manufacturing plants is also discussed.

#### *Step 2: Mixing of powders, drying, pressing, presintering, shaping, and sintering of hard metals*

Step 2 involves mixing of the powders, drying, pressing, presintering, shaping of the presintered hard metal, and sintering and generally seems to be associated with the highest airborne exposures to both cobalt and tungsten. For the studies summarized in Table 2-3, the highest levels of cobalt in air were reported from one of the two plants studied by Sprince *et al.* (1984) in the United States during weighing and mixing of powders (mean = 32,740 μg/m$^3$; range = 44 to 438,000 μg/m$^3$), the same plant also had high concentrations of cobalt in air for milling operations (mean = 8,661 μg/m$^3$; range = 91 to 48,148 μg/m$^3$) followed by pressing (mean = 755 μg/m$^3$; range = 13 to 7,359

μg/m$^3$). For the second plant, the highest levels were also for weighing and mixing of powders (mean = 327 μg/m$^3$; range = 20 to 1,480 μg/m$^3$) and milling (mean = 282 μg/m$^3$; range = 15 to 800 μg/m$^3$). Mean levels were also high for pressing (326 μg/m$^3$) and drying (337 μg/m$^3$).

A more recent study of exposures in the United States (Stefaniak *et al.* 2007) reported relatively low levels (ranging from 9 to 145 μg/m$^3$) for cobalt in air for powder mixing, spray drying, screening, and pressing, and the authors of this study noted that the levels of airborne cobalt were low relative to historical levels published during the 1980s and 1990s. The levels associated with Step 2 processes reported between 1984 and 2007 were highest for pressing or shaping/forming operations (range = 48 to 5,270 μg/m$^3$) in studies for companies in Japan (Kumagai *et al.* 1996, Kusaka *et al.*1986b, Kusaka 1996, Ichikawa *et al.* 1985) and Italy (Sala *et al.* 1994).

Tungsten air levels were only reported by Kraus *et al.* (2001), Sabbioni *et al.* (1994a), and NIOSH (1977). Kraus reported a maximum value for tungsten (97.4 μg/m$^3$) during forming operations with much lower levels for sintering operations (5.9 and 12.9). Sabbioni *et al.* reported a maximum mean tungsten airborne level of 150 μg/m$^3$ during weighing operations; however, the maximum mean level of airborne tungsten considered respirable [< 7 μm] was 3.1 μg/m$^3$. For powder mixing operations, Sabbioni *et al.* reported a maximum tungsten level of 210 μg/m$^3$ (mean = 26 μg/m$^3$). A review by NIOSH (1977) reported much higher tungsten air levels for powder processing (880 to 25,600 μg/m$^3$), casting operations (520 to 17,600 μg/m$^3$), and forming operations (80 to 26,700 μg/m$^3$); however, very limited additional information was provided, and some data were inconsistent within the report. The report noted that the regulatory limit of 6 mg/m$^3$ was rarely exceeded in these operations; [therefore, the higher levels likely occurred infrequently].

In a study characterizing exposure to cemented tungsten carbide workers, Day *et al.* (2008) used surface wipe samples to assess surface contamination and skin exposure to cobalt, chromium, and nickel in three cemented tungsten carbide production facilities, each specializing in a specific aspect of cemented tungsten carbide production: i.e., metal reclamation; powder handling; and forming, shaping, sintering, grinding, and sandblasting operations (production). The highest geometric mean cobalt levels from skin wipes were observed among workers at the powder handling facility (hands = 388 μg, necks = 55 μg). Across four work areas involved in production operations within the powder handling facility, geometric mean cobalt levels ranged from 442 μg (screening) to 1,328 μg (powder mixing) for workers' hands and from 64 μg (milling) to 342 μg (powder mixing) for workers' necks. Within the production facility for Step 2 work areas, cobalt levels ranged from 69 μg (pressing) to 170 μg (extrusion) for workers' hands and from 2.7 μg (pressing) to 12 μg (tray preparation) for workers' necks.

### *Reclamation (recycling) of hard metals*

Two studies in the United States (Sprince *et al.* 1984, Stefaniak *et al.* 2007) reported air concentrations for reclamation of hard-metal scrap. Sprince *et al.* reported a range of 114

to 1,708 μg/m$^3$ for the two plants that they studied, while Stefaniak *et al.* reported a range of 21 to 192 μg/m$^3$ for the reclamation operations including scrap loader, ball mill, and large and small crusher.

Within the metal reclamation facility studied by Day *et al*. (2008) (see above), across four production work areas, geometric mean cobalt dermal-wipe levels ranged from 57 μg (carbide production) to 443 μg (metal separation) for workers' hands and from 4.3 μg (carbide production) to 693 μg (metal separation) for workers' necks.

### *Miscellaneous operations*

A few papers reported exposure data for jobs outside of the production process. McDermott *et al.* (1971) reported air concentrations of cobalt 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 (including housekeeping) activities were reported by Scansetti *et al.* (1985) to result in exposure greater than 50 μg/m$^3$, while Kraus *et al.* (2001) reported urinary levels associated with maintenance of 1.3 to 4.7 μg/L for cobalt and 1.5 to 5.3 μg/L for tungsten. Pellet *et al.* (1984, as reported by Angerer and Heinrich 1988) reported exposures for a category of "using hard metals" ranging from 180 to 193 μg/m$^3$ for air and a mean of 11.7 μg/L for urine.

Day *et al*. (2008) provided dermal exposure levels for a number of work areas outside of the production processes within 3 different cemented carbide manufacturing facilities. The work areas included maintenance, administration, inventory control, and shipping (both product and powder shipping). Cobalt levels from workers' hands ranged from 4.1 μg (administrative) to 425 μg (maintenance) and from 0.5 μg (administrative) to 35 μg (maintenance).

**Table 2-3. Hard-metal exposure levels from pre-sintering and sintering operations (Step 2) (levels are for cobalt unless otherwise noted)**

| Stage of the hard-metal production process | Air concentration[a] mean (range) μg/m$^3$ {N} | Biological levels[a] mean (range) μg/L {N} | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Scrap reclamation, powder mixing, drying, screening, pressing | 9–192 {9} (range of single measurements across operations) | NA | Highest levels for scrap reclamation & pressing; lowest for drying<br>Highest respirable mass percentage for powder mixing; lowest for scrap reclamation | Stefaniak *et al.* 2007<br>(USA, NR) |
| Powder processing, forming, pressing, sintering, maintenance | *Cobalt*<br>NR (0.61–343) {15}<br>*Tungsten*<br>NR (5.3–254) {15} | *Cobalt*<br>4.1–28.5 (0.19–227.8) {75}<br>*Tungsten*<br>3.4–12.5 (0.33–168.6) {75} | Highest mean Co air level for sintering; lowest for forming<br>Highest mean W air level for powder processing; lowest for pressing<br>Highest urinary Co level for powder processing (227.8 μg/dL); lowest for sintering (0.31 μg/dL)<br>Highest urinary W level for pressing (71.0 μg/dL); lowest for forming (0.33 μg/dL) | Kraus *et al.* 2001<br>(Germany, NR) |
| Powder preparation, pressing, shaping, sintering | 24–459 (1–6,390) {393} | NA | Highest levels for powder preparation; lowest for sintering | Kumagai *et al.* 1996<br>(Japan, NR) |
| Shaping, sintering | 25 & 141 (7–436) {27} | Urine: 1 & 2 {NR}<br>Blood (μg/dL): 0.28 & 0.42 {NR}<br>Hair (ppm): 25.8 (shaping) {NR} | Higher Co air and blood levels from shaping | Kusaka 1996<br>(Japan, NR) |

| Stage of the hard-metal production process | Air concentration[a] mean (range) μg/m$^3$ {N} | Biological levels[a] mean (range) μg/L {N} | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Powder mixing | *Cobalt*<br>240 (19–1,320) {70}<br>170 (20–350) {23}<br>*Tungsten*<br>26 (3–210) {23} | *Cobalt*<br>61.1 (13–262) {23}<br>*Tungsten*<br>2.29 (0.25–12.5) {23} | Co levels include assessments of 70 workers for cobalt alone and assessments for a subset of 23 workers for Co and W exposure levels | Sabbioni *et al.* 1994a<br>(Pavia, Italy, NR) |
| Mixing, forming, pressing | *Before*<br>82–772 (40–5,270) {23}<br>*After*<br>29–82 (12–190) {31} | NA | "Before" and "After" installation of ventilation controls<br>Highest mean (geometric) levels for forming; lowest for pressing | Sala *et al.* 1994<br>(Italy, NR) |
| Mold filling, sintering, mechanical working, tool production, hard-metal alloy filling | 2–382 (0.8–2,600) {250} | 4.8–587 (0.8–2,100) {NR} | Range of medians<br>Highest levels for mold filling; lowest for hard-metal alloy filling | Mosconi *et al.* 1994<br>(Italy, 1991) |
| Powder preparation, pressing, shaping, sintering | 28–688 (2–6,388) {251} | NA | Highest levels for powder preparation; lowest for sintering | Kusaka *et al.* 1986b<br>(Japan, 1981–4) |
| Sawing, pressing/mixing, sintering, supervision, office work | 4.3 (0.3–15) mg/m$^3$ dust {NR}<br>Cobalt content ranged from 4% to 17% | *Urinary cobalt levels*<br>4.6–64.3 (0.3–102) {22}<br>*Serum cobalt levels*<br>< 0.3–18.3 (< 0.3–32) {22} | Highest urinary and serum Co levels for sawing operations; lowest for office workers<br>Authors noted a daily load of about 3 mg cobalt per day | Posma and Dijstelberger 1985<br>(The Netherlands, NR) |
| Powder handling, pressing, shaping, sintering, office workers | 28–367 (4–859) {93} | *Urinary cobalt levels*<br>2–235 (1–392) {113}<br>*Blood cobalt levels*<br>0.19–1.87 (0.08–5.30) {113} | Highest urine and blood mean Co levels for rubber press operators; lowest levels for office workers<br>Highest Co air level of 1,203 μg/m$^3$ reported for a worker using a respirator for an unspecified task | Ichikawa *et al.* 1985<br>(Japan, NR) |

| Stage of the hard-metal production process | Air concentration[a] mean (range) μg/m$^3$ {N} | Biological levels[a] mean (range) μg/L {N} | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Pressing, forming, sintering, finishing (testing), maintenance | NR (< 10 to > 100) {NR} | Monday: up to 36 {26}<br>Friday: up to 63 {26} | Highest levels for hand pressing; lowest for sintering | Scansetti *et al.* 1985<br>(Italy, NR) |
| Weighing & mixing, milling, drying, pressing, machining, reclaiming | 94–32,470 (2–438,000) {138} | NA | Highest levels for weighing & mixing; lowest for machining<br>Sampling conducted in a manner to obtain peak levels | Sprince *et al.* 1984<br>(USA, NR) |
| Using hard metal | NR (180–193) {NR} | 11.7 (NR) {NR} | No additional information provided | Pellet *et al.* 1984 as cited in Angerer and Heinrich 1988<br>(NR, NR) |
| Powder mixing, pressing, general maintenance | 25–48 (NR) {NR} | NA | Highest levels for powder mixing; lowest for general maintenance | NIOSH 1981<br>(USA, 1977–8) |
| Powder processing, tool & die operations, casting, forming | *Cobalt*<br>NR (0–6,800) {NR}<br>*Tungsten*<br>NR (80–26,700) {NR} | NA | Highest Co air levels for casting; lowest for both powder processing and casting<br>Highest & lowest W air levels both reported for forming | NIOSH 1977<br>(United States, Austria, Switzerland, Sweden, former USSR, NR) |
| 18 different operations across the manufacturing process | NR (0–6,700) {169} | NA | Highest Co air levels for miscellaneous operations; lowest (0 μg/m$^3$) reported for metal preparation, press operations, surface grinding, and drilling operations | McDermott 1971<br>(USA, NR) |

| Stage of the hard-metal production process | Air concentration[a] mean (range) μg/m$^3$ {N} | Biological levels[a] mean (range) μg/L {N} | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Powder processing<br><br>Tool and die operations | P: 1,050–1,670 (NR) {NR}<br>A: 120–220 (NR) {NR}<br>P: 50–230 (NR) {NR}<br>A: 10–70 (NR) {NR} | NA | P = worker personal exposure levels<br>A = general atmosphere exposure levels<br>N = 977 total samples<br>Two simultaneous samples were taken; one at the breathing level of the worker ( "P") and the other in the isle between machines to represent general atmosphere levels ("A"). | Fairhall *et al.* 1949 (USA, NR) |

Co = cobalt; N = number of samples; NA = not assessed; NR = not reported; W = tungsten.
[a] Cobalt levels unless otherwise noted.

### *2.3.6 Exposure during finishing of sintered hard-metal products (Step 3)*

The final step in hard-metal manufacturing consists of various finishing operations as illustrated in Step 3 of Figure 2-1, and this section discusses occupational exposure associated with those processes. Important exposure determinants with exposure levels presented in Table 2-4 are discussed first, followed by engineering controls to reduce exposures, and the findings on the respirable fractions for cobalt and tungsten in dust.

#### *Exposure levels during finishing of sintered hard-metal products*

Post-sintered products are often finish-ground or sharpened at the production facility to specified dimensions or characteristics. Hard-metal products also may require maintenance and sharpening after use. In fact, in 1995 the Washington State Department of Labor and Industries warned that workers who file saw blades and those who machine tools made of hard metal may be exposed to toxic levels of cobalt (WSDLI 1995). This section discusses exposures that occur both from finish operations at the production facility, and from grinding and resharpening operations after use. [Since both procedures involve grinding or sharpening of post-sintered products, there should be no appreciable difference in the chemical or physical properties between the dusts generated.] These exposures may occur at facilities that produce both the cobalt–tungsten carbide hard metal and the end-use hard-metal products, at small businesses that recondition dull or broken hard-metal tools, or in tool reconditioning or machining shops within larger businesses that use hard-metal tools (for example, lumber mills often employ full-time saw sharpeners).

Sesana *et al.* (1994) noted that the assessment of exposure from grinding hard-metal tools has not received satisfactory attention from industrial hygienists, probably because the industry consists of small facilities that usually employ relatively few workers (generally fewer than 10 workers). Exposure circumstances may vary for the same job type based on the size of a company. In small workshops that mainly perform sharpening operations, grinders will often be exposed for 6 to 8 hours per day, while in large metallurgical and mechanical industries where operations are carried out in tool or machine shops, exposure generally will range from 30 minutes to 3 or 4 hours per day (Imbrogno and Alborghetti 1994). Exposure from this industrial segment has the potential to be extensive. Although data from the U.S. Economic Census and the Annual Survey of Manufacturers indicated that in 2002 there were 3,461 sawmills in the United States, employing 95,452 workers (USDC 2005), no breakdown of these data was provided to identify how many of these workers were employed in tool maintenance or grinding operations that could result in exposure to cobalt–tungsten carbide. However, sawmills are only one segment of the industries that perform sharpening and grinding operations on hard-metal products.

The operations that are discussed in this section include primarily grinding and sharpening operations, including both wet-grinding and dry-grinding processes. Other hard-metal finishing processes include blasting and electron discharging (Kumagai *et al.* 1996, Kusaka *et al.* 1986b) (see Table 2-2); however, these processes result in cobalt air concentrations that are one to four orders of magnitude less than grinding operations. Kraus *et al.* (2001) reported higher levels from dry grinding when compared with wet

grinding. (See below for a further discussion of exposure issues associated with wet-grinding.) In Table 2-4, if the study authors reported the type of grinding process that was used, that information is included, [but most studies did not specify the grinding process used].

Table 2-4 also provides some information on total dust levels from grinding operations and associated levels of cobalt (Koponen *et al.* 1982, Linnainmaa *et al.* 1996, Posma and Dijstelberger 1985, Stefaniak *et al.* 2007) and tungsten (Koponen *et al*. 1982). Cobalt levels generally were less than 10% of the total dust (Stefaniak *et al*. 2007, Linnainmaa *et al*. 1996, Posma and Dijstelberger 1985, Koponen *et al*. 1982); although Posma and Dijstelberger reported the upper end of the range to be 17%. Koponen *et al*. (1982) reported that tungsten levels in dust ranged from 66% to 73%. Stebbins *et al.* (1992) reported that the airborne tungsten concentrations in all 3 samples collected in the dry- and wet-grinding departments of a small company producing carbide-tipped saw blades ranged from 410 to 710 μg/m$^3$.

The biological monitoring data that are presented in Table 2-4 consist primarily of cobalt levels in urine; however, data also were reported for tungsten in urine (Goldoni *et al*. 2004, Kraus *et al*. 2001, Sabbioni *et al*. 1994a, Della Torre *et al*. 1990) and/or cobalt in blood (Della Torre *et al.* 1990, Ichikawa *et al.* 1985, Kusaka 1996, Sabbioni *et al.* 1994a), hair (Kusaka 1996, Sabbioni *et al*. 1994a) and toenails (Sabbioni *et al*. 1994a) (see Appendix B, Table B-2). Biological data presented in Table 2-4 generally show higher levels in exposed subjects versus unexposed controls (Goldoni *et al.* 2004, Ichikawa *et al.* 1985, Posma and Dijstelberger 1985), in levels assessed later in the week when compared with earlier in the week (Sesana *et al.* 1994), and in post-shift levels when compared with pre-shift levels (NIOSH 1987a, 1987b); however, these differences were usually reflected in higher associated air levels that were measured in concert with the biological levels. (See Section 2.4 for a more detailed discussion of biological indicators of exposure.)

Higher exposure levels have been seen in wet-grinding operations compared with dry-grinding operations in some studies (Imbrogno and Alborghetti 1994, Stebbins *et al.* 1992), but wide variations in cobalt levels in metal-working fluids for wet grinding of hard metals have been reported, [and no data were found on tungsten levels in metal-working fluids] (Kennedy *et al.* 1995, NIOSH 1987a, 1987b, Stebbins *et al.* 1992, Teschke *et al.* 1995). Cobalt in hard-metal wet-grinding metal-working fluids has been shown to exist both as dissolved cobalt and suspended with carbide particles in the metal-working fluids (Stebbins *et al.* 1992).

In a study characterizing exposure to cemented tungsten carbide workers, Day *et al.* (2008) used surface wipe samples to assess dermal exposure to cobalt in the three cemented tungsten carbide production facilities, each specializing in a specific aspect of cemented tungsten carbide production (see Section 2.3.5). For Step 3 job categories within the cemented carbide production facility, Day *et al*. (2008) presented cobalt levels ranging from 23 μg (sandblasting) to 123 μg (breakdown) for workers' hands and from 2.5 μg (sandblasting) to 17 μg (breakdown) for workers' necks.

*Engineering controls to limit exposure*

Several studies have assessed the effects of engineering controls, in particular local exhaust ventilation systems, and their long-term effectiveness in controlling airborne cobalt levels. A number of studies have reported levels that exceeded regulatory limits or NIOSH guidelines before the installation of ventilation systems, with reductions to levels below the regulatory or guideline limits after ventilation systems were installed (Lichtenstein *et al.* 1975, Paulsen and Kilens 1994, Sala *et al.* 1994, Simcox *et al.* 2000). However, levels exceeding regulatory limits were measured even after controls were installed in the study by Sala *et al.* (1994). Although drastic reductions of cobalt exposure levels were seen after the installation of ventilation systems, Simcox *et al.* (2000) nonetheless concluded that airflow associated with the ventilation systems alone did not guarantee low exposures, and that proper hood design and worker acceptance and proper use of the hoods were important factors impacting exposure levels.

*Respirable mass*

Only a portion of the total air levels of dust or cobalt from finishing operations represent respirable mass (Kusaka *et al.* 1992, Linnainmaa *et al.* 1996, NIOSH 1987a, 1988, Sabbioni *et al.* 1994a, Stebbins *et al.* 1992, Stefaniak *et al.* 2007). The percentage of respirable mass for cobalt and tungsten varied widely even between methods that reported the same particle-size cutoff value. Kusaka *et al.* (1992) and Sabbioni *et al.* (1994a) both used a particle-size cutoff of < 7 μm, but Kusaka *et al.* reported that cobalt in the respirable fraction was 70.1% of that in total dust for air samples from a hard-metal grinding worksite, while Sabbioni *et al.* reported that dry-grinding operations in their study had cobalt in the < 7 μm fraction that ranged from 3.7% to 11.3%. Intermediate values (ranging between approximately 13% and 30%) were reported by Stebbins *et al.* (1992), NIOSH (1988), and NIOSH (1987a), but the cutoff value was not specifically defined in these studies.

### *2.3.7 Exposure to end-users (other than grinders or sharpeners)*

Pellet *et al.* (1984, as cited in Angerer and Heinrich 1988) reported a range of 180 to 193 μg/m$^3$ cobalt air levels and a mean urinary cobalt level of 11.7 μg/L associated with using hard metal; however, no additional information was provided for these data. No other information was located that directly demonstrated exposure to hard metals for 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).

Alcaraz (2004) assessed occupational exposure to hard-metal particulates for 11 different shops in the state of Washington that were characterized as either saw manufacturers, saw repair shops, or saw mills. This study showed that saw mills had the lowest exposures of the three types of operations assessed. The exposure assessment included three control machine shops that did not grind hard metals. The mean cobalt level for hard-metal exposed workers (N = 141; samples from 78 exposed workers) was 20.2 μg/m$^3$ (range:

0.7 to 279 μg/m$^3$) and 7% were above 50 μg/m$^3$. The machining (control) shops had low cobalt concentrations (mean = 1.2 μg/m$^3$; range = 0.4 to 4 μg/m$^3$).

**Table 2-4. Hard-metal exposure levels from post-sintering operations (includes exposures from Step 3 of the manufacturing process and from tool repair and maintenance after manufacture) (levels are for cobalt unless otherwise noted)**

| Operation | Air concentration Mean (Range) ($\mu g/m^3$) {N} | Biological Levels[a] Mean (Range) ($\mu g/L$) {N} | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Dry grinding and adjacent area | 1.0 & 1.0{2} | NA | Both areas had a cobalt concentration of 1 $\mu g/m^3$ based on one sample for each | Stefaniak *et al.* 2007 (USA, NR) |
| Powder mixing or dry grinding | *Cobalt*[b] 8.25–26.0[c] (0.1–37.4) {NR} *Tungsten*[b] < 0.01–3.0[c] (< 0.01–4.9) {NR} | *Cobalt*[d] [0.05–26[c] (0.03–190)[e]] {49} *Tungsten*[d] [< 0.1–13.4[c] (< 0.1–26.4)[e]] {49} | Data across three factories; two factories included workers performing both grinding and powder mixing; maximum values for the workers who performed only grinding | Goldoni *et al.* 2004 (Italy, NR) |
| Wet and dry grinding | *Cobalt* 0.2 & 0.48 {2} *Tungsten* 3.3 & 81.3 {2} | *Cobalt* 2.2 (0.19–6.0) {5} *Tungsten* 94.4 (10.6–168.6) {5} | Maximum air values for dry grinding operations; type of grinding process not specified for urine analysis results | Kraus *et al.* 2001 (Germany, NR) |
| Hard-metal and stellite[f] grinding, brazing, and welding | A: 51–146 (10–346) {12} B: 8–26 (3–63) {41} | NA | "A" = levels before ventilation installed, "B" = levels after ventilation installed Includes data for grinding of both stellite[f] and hard metals | Simcox *et al.* 2000 (USA, 1995) |
| Grinding hard-metal and stellite[f] | NR ({1–70}) {91} | 14.2 (0.5–160) {131} | Measurements from 16 workplaces.; air range estimated from graph Includes data for grinding of both stellite[f] and hard metals | Linnainmaa and Kiilunen 1997 (Finland, NR) |
| Tool manufacturing and blade repair | 17[g] (2–240) {87} | NA | Includes data for grinding of both stellite[f] and hard metals | Linnainmaa *et al.* 1996 (Finland, NR) |
| Blasting, electron discharging, grinding | 2–45 (1–482) {542} | NA | Maximum levels from grinding | Kumagai *et al.* 1996 (Japan, NR) |

| Operation | Air concentration Mean (Range) (μg/m$^3$) {N} | Biological Levels[a] Mean (Range) (μg/L) {N} | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Grinding | 31 & 36 (2–40) {13} | Urine: 9 & 29 {2}<br>Blood: 0.32 & 0.4 (μg/dL) {2}<br>Hair: 3.42 & 9.11 (ppm) {2} | Data are for two grinders | Kusaka 1996<br>(Japan, NR) |
| Grinding hard-metal blades | A: NR (1–160) {87}<br>B: NR (< 2–28) {43} | A: NR (6.1–63) {26}[h]<br>B: NR (0.4–62) {20}[h] | "A" = levels before ventilation installed, "B" = levels after ventilation installed | Linnainmaa 1995<br>(Finland, NR) |
| Grinding hard-metal and stellite[f] saws | 9 (< 0.64–106) {278} | NA | Data are from personal sampling for 112 workers<br>Includes data for grinding of both stellite[f] and hard metals | Teschke *et al.* 1995<br>(Canada, 1991) |
| Grinding operations | [89.5] (26.4–202.8) {10} | NA | After engineering controls installed, maximum value fell to < 1 μg/m$^3$ | Paulsen and Kilens 1994<br>(USA, 1990) |
| Grinding operations | 5–230[c] (1.5–690) {NR} | 31.5 & 151 (0.8–730) {NR} | Includes both personal and stationary sampling results across multiple facilities | Mosconi *et al.* 1994<br>(Italy, 1991) |
| Grinding and sharpening operations | 0.0036–0.350 (NR) {23} | 0–40.25 (0–86) {48} | Analysis of 12 manufacturing facilities | Imbrogno and Alborghetti 1994<br>(Italy, NR) |
| Wet grinding (3 factories) | 6.4–376[g] (NR) {60} | 15.3–138.3 (NR) {22} | Mean level at facility with maximum level fell to 9.9 μg/m$^3$ after ventilation installed | Sesana *et al.* 1994<br>(Italy, NR) |
| Hard-metal tool grinding | w/o: 91[g] & 40[g] (5.0–1,338) {103}<br>w: 9[g] & 12[g] (1.0–58) {102} | NA | "w/o"= plants without ventilation system.<br>"w"= plants with ventilation system | Sala *et al.* 1994<br>(Italy, NR) |
| Sharpening operations | 10[g] (4–70) {15} | NA | Noted as before ventilation control installed; no data provided for after | Sala *et al.* 1994<br>(Italy, NR) |
| Grinding and sharpening | NA | 17 nmol/mmol CR (NR) {~150} | 19 nmol/mmol CR presented for hard-metal manufacturing which included pre-sintering operations and post-sintering grinding | White and Dyne 1994<br>(U.K., NR) |

| Operation | Air concentration Mean (Range) (μg/m$^3$) {N} | Biological Levels[a] Mean (Range) (μg/L) {N} | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Hard-metal tool grinding facilities | w/o: 6.68[g] & 47.75[g] (NR) {34}<br>w: 3.47[g] & 4.43[g] (NR) {23} | w/o: 28.5[g] ± 3.97[i] (NR) {6}<br>w: 2.66[g] ± 1.69[i] (NR) {8} | "w/o"= plants without aspirators<br>"w"= plants with aspirators | Cereda *et al.* 1994<br>(Italy, NR) |
| Grinding (across 2 factories) | *Cobalt*<br>64–985 (NR) {NR}<br>< 7 μm: 4–14 (NR) {NR}<br>*Tungsten*<br>2.1–77 (NR) {NR}<br>< 7 μm: 0.13–2.4 (NR) {NR} | CoB: 45.6 (1–245) {88}<br>CoU: 303.6 (0.75–5,500) {88}<br>CoH: 49,088 (110–910,000)[j] {90}<br>CoN: 53,792 (109–580,000)[j]{92}<br>WB: 1.2 (0.04–6.5) {43}<br>WU: 6.7 (0.11–230) {78}<br>WH: 2,147 (25–59,000)[j]{75}<br>WN: 3,056 (27–105,000)[j]{82} | < 7 μm is the concentration in the air fraction measuring less than 7 μm (considered respirable) measured by stationary sampling.<br>Biological data were aggregated and summarized across all workers irrespective of production stage or factory | Sabbioni *et al.* 1994a<br>(Bergamo Province, Italy, NR) |
| Grinding operations | *Total cobalt*<br>27–[87.4] (NR) {43}<br>*Respirable cobalt*<br>11 (2–28) {24}<br>*Total tungsten*<br>NR (410–710) {3} | 12.2 & 33.6 (2.6–38) {19} | Levels across 4 datasets (1 dataset for respirable Co). High urinary level for wet grinding, low level for dry grinding | Stebbins *et al.* 1992<br>(USA, NR) |
| Grinding operations | 32 (1–440) {133} | NA | 66% of total dust was respirable (< 7 μm), and 70.1% of total cobalt was respirable | Kusaka *et al.* 1992<br>(Japan, NR) |
| Sharpening and grinding operations | NA | Urine: [14.17] (2.5–35) {6}<br>Blood: [4.0] (1.5–9) {6}<br>*Tungsten*<br>Urine: [192] (2–1,000) {6}<br>Blood: [10.8] (0.9–60) {60} | Levels from 4 workers, one of whom developed terminal hard-metal pneumoconiosis; maximum levels all from the terminal patient except Co in urine | Della Torre *et al.* 1990<br>(Italy, NR) |
| Grinding, sharpening, and tooling | *Cobalt*<br>Respirable: 4 (ND–4) {31}<br>Total: 30.2 (ND–97) {33} | NR (ND–7.6) (63} | Only thirty percent of urine samples exceeded detection limit | NIOSH 1988<br>(USA, NR) |

| Operation | Air concentration Mean (Range) (μg/m$^3$) {N} | Biological Levels[a] Mean (Range) (μg/L) {N} | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Saw blade and tool sharpening | [9.38–45] (2.8–63) {7}<br>*Tungsten*<br>[186 & 645] (ND–925) {6} | 2.74–18.3 (ND–23.8) {48}<br>*Tungsten*<br>NA | Data across several groups of workers. Minimum cobalt level from an office worker control group | NIOSH 1987b<br>(USA, NR) |
| Finish grinding of hard-metal | *Cobalt*<br>Respirable: [4.3] (ND–8.4) {24}<br>Total: 13.5 (ND–26.8) {24}<br>*Tungsten*<br>280 (ND–410) {24} | *Pre-shift*<br>10.5 (4.7–19)[d] {10}<br>*Post-shift*<br>18.09 (8.4–27.7)[d] {10} | Respirable airborne cobalt was significantly associated with post-shift urinary cobalt levels ($P$ = 0.003)<br>[Tungsten in air assumed to be total level] | NIOSH 1987a<br>(United States, NR) |
| Blasting, electron discharging, grinding | 3–1,292 (1–1,471) {217} | NA | Wet grinding mean was 53 μg/m$^3$, dry grinding mean was 1,292 μg/m$^3$ | Kusaka *et al.* 1986b<br>(Japan, 1981–1984) |
| Wet-grinding | 44–317 (3–1,203) {107} | Urine: 17–68 (1–265) {107}<br>Blood: 3.3–6.5 (1–39) {107} | Maximums for air and blood from workers who used respirators | Ichikawa *et al.* 1985<br>(Japan, NR) |
| Grinding operations | Dust: 4.3 (0.3–15) mg/m$^3$ {NR}<br>Co ranged from 4% to 17% | 25.5 (5.8–39)[d] {10} | Biological data specific for employees who performed grinding operations, although air data reflect dust samples taken from various parts of the factory | Posma and Dijstelberger 1985<br>(The Netherlands, NR) |
| Grinding operations | 17 & 118 (3–307) {13} | NA | Sampling was conducted in a manner to obtain peak exposure levels. | Sprince *et al.* 1984<br>(USA, NR) |
| Grinding operations in a hard-metal plant | *Dust*<br>2,100 (1,500–3,000) {4}<br>*Cobalt*<br>7%–9% of dust concentration<br>*Tungsten*<br>66%–73% of dust concentration | NA | Only cobalt and tungsten content of dust presented [concentration not presented]; range is based on results from two analytical techniques | Koponen *et al.* 1982<br>(Finland, NR) |
| Grinding operations | 19 (NR) {NR} | NA | No additional information provided | NIOSH 1981<br>(NR, 1977–1978) |
| Dry grinding without exhaust | NR (40–2,440) {NR} | NA | No additional information provided | NIOSH 1977<br>(Switzerland, NR) |

| Operation | Air concentration Mean (Range) (μg/m$^3$) {N} | Biological Levels[a] Mean (Range) (μg/L) {N} | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Wet grinding | 240 & 280 (30–930) {37}<br>*Tungsten*<br>3,930 & 5,160 (< 200–12,800) {37} | NA | Two sets of data based on personal or stationary sampling | Lichtenstein *et al.* 1975<br>(United States, NR) |

Co = cobalt; CoA = cobalt in air; CoB = cobalt in blood; CoH = cobalt in hair; CoN = cobalt in toenails; CR = creatinine; N = number of samples; NA = not assessed; ND = not detected, below the limit of quantitation; NR = not reported; W = tungsten; WA = tungsten in air; WB = tungsten in blood; WH = tungsten in hair; WN = tungsten in toenails.

[a] Urinary levels unless otherwise noted.

[b] In the original article, units were incorrectly stated to be mg/m$^3$ rather than μg/m$^3$ (personal communication from A. Mutti).

[c] Median.

[d] μg/g creatinine.

[e] Interquartile range.

[f] See glossary for definition of stellite. The authors of these studies did not distinguish between exposure to stellite and to cobalt–tungsten carbide hard metals so the data include exposures from grinding both materials.

[g] Geometric mean.

[h] Original data in units of nmol/L, converted to μg/L using the conversion factors 1 nmol/L = 58.9 ng/L (Goldoni *et al.* 2004), and 1 ng/L = 0.001 μg/L.

[i] Geometric standard deviation.

[j] ng/g.

### *2.3.8 Non-process–specific exposure data for hard-metal production*

Several studies presented occupational exposure data for hard-metal production without providing detail regarding the production stage where the exposure took place (Angerer and Heinrich 1988, Gallorini *et al.* 1994, Lison *et al.* 1994, NIEHS 2002, Sabbioni *et al.* 1994a, Sala *et al.* 1994, Scansetti *et al.* 1998, Torra *et al.* 2005). Table 2-5 presents these non-process–specific occupational exposure data for hard-metal production.

Urinary cobalt levels for hard-metal workers have been seen to increase through the workday (Torra *et al.* 2005) and workweek (Torra *et al.* 2005, Scansetti *et al*. 1998, Lison *et al*. 1994). Torra *et al.* (2005) reported that 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. In all cases, workplace air concentrations were higher than the ACGIH Threshold Limit Value (TLV) of 20 μg/m$^3$, and the authors reported that 85% of the workers analyzed had urinary cobalt levels that exceeded the ACGIH BEI level of 15 μg/L.

Sala *et al.* (1994) assessed air level reductions due to the installation of ventilation. The authors noted that substantial air level reductions were seen across all stages of the hard-metal manufacturing process with significant reductions seen in grinding operations (see Section 2.5.3).

Among a group of patients occupationally exposed to hard metals who presented with asthma and/or fibrosis, Sabbioni *et al*. (1994a) reported cobalt levels in bronchoalveolar lavage (BAL) ranging from less than 0.7 to 10.1 μg/L (12 patients) and 0.2 to 7 μg/L for tungsten (10 patients). Open lung biopsy was performed on two patients with wet-weight levels of 830 and 2,440 ng/g for cobalt, and 52,000 and 107,000 ng/g for tungsten. Transbronchial biopsy was performed on 5 patients with wet-weight levels ranging from 1,900 to 15,000 ng/g for cobalt, and 33,900 to 134,000 ng/g for tungsten.

**Table 2-5. Non-process–specific exposure levels in air and biological samples**

| Type of exposure (Year of measurement) | Air concentration[a] Mean (range) {N} (μg/m$^3$) | Concentration in biological samples[a] Mean (range) {N} (μg/L) | Reference (Location) |
|---|---|---|---|
| Hard-metal manufacture (NR) | 100 (79–130) {3} | *Worker urine*<br>46 (11–110) μg/g CR {19}<br>*Unexposed control urine*<br>1.2 (1.1–1.5) μg/g CR {50} | Torra *et al*. 2005 (Spain) |
| Hard-metal manufacture (NR) | Mon.: 21.16 (11–56) {6}<br>Thu: 31.66 (7–92) {6} | *Urine*<br>13.23 (2.58–29.8) {6}<br>30.87 (8.17–62.6) {6} | Scansetti *et al*. 1998 (Italy) |

| Type of exposure (Year of measurement) | Air concentration[a] Mean (range) {N} (μg/m$^3$) | Concentration in biological samples[a] Mean (range) {N} (μg/L) | Reference (Location) |
|---|---|---|---|
| Hard-metal tool production (mixing, sintering, grinding) (NR) | NA | CoU: 13.9 (1.2–309) {24}<br>CoB: 5.06 (0.7–12.5) {20}<br>CoH: 9,607 (1,050–29,900)[b] {22}<br>CoN: 18,904 (2,000–109,000)[b] {23}<br>WU: 9.32 (1.1–25.5) {21}<br>WB: 1.29 (0.11–10) {16}<br>WH: 7,018 (227–76,000)[b] {20}<br>WN: 17,298 (1,070–127,000)[b] {23} | Sabbioni *et al*. 1994a (Milan, Italy) |
| Hard-metal pressing, forming, sintering, finishing, testing (NR) | NA | CoU: 32.5 (0.3–150) {28}<br>CoH: 13,390 (805–13,600)[b] {28}<br>WU: 12.8 (0.35–55) {24}<br>WH: 9,585 (340–40,000)[b] {24} | Sabbioni *et al*. 1994a (Turin, Italy) |
| Hard-metal manufacture (NR) | Mon.: 9[c] (2–127) {10}<br>Fri.: 19[c] (1–203) {10} | *Urine*<br>13.1[c] (3.1–87.5) μg/g CR {10}<br>17.6[c] (3.0–85.6) μg/g CR {10} | Lison *et al*. 1994 (Belgium) |
| Four groups of heavily exposed hard-metal workers (NR) | NA | *Workers urine (4 groups)*<br>189–1,254 (NR) {20}<br>*Unexposed controls urine*<br>0.85 (NR) {5} | Gallorini *et al*. 1994 (Italy) |
| Hard-metal workers, ranges from 3 studies (NR) | (NR) 9–13,600 {NR}<br>(NR) 10–60 {NR}<br>(NR) 1–11,000 {NR} | NA | NIEHS 2002 (NR) |
| Medium-sized hard-metal plant before and after ventilation added in 1991 | *Before*<br>428 (139–978) {21}<br>*After*<br>14 (6–40) {7} | NA | Sala *et al*. 1994 (Italy) |
| Hard-metal-producing industry (2 subgroups) (NR) | (a) 90 (NR) {NR}<br>(b) 10 (NR) {NR} | *Blood*<br>(a) 10.5 (NR) {NR}<br>(b) 0.7 (NR) {NR}<br>*Urine*<br>(a) 134 (NR) {NR}<br>(b) ~ 3 (NR) {NR} | Alexandersson and Lidums 1979 as cited in Angerer and Heinrich 1988 (Russia) |

CoB = cobalt in blood; CoH = cobalt in hair; CoN = cobalt in toenails; CoU = cobalt in urine; CR = creatinine; N = number of samples; NA = not assessed; WA = tungsten in air; WB = tungsten in blood; WH = tungsten in hair; WN = tungsten in toenails; WU = tungsten in urine.

[a] Levels are for cobalt unless otherwise noted.

[b] ng/g.

[c] Geometric mean.

## 2.4 Biological indicators of exposure

The American Conference of Governmental Industrial Hygienists (ACGIH) lists both urinary and blood concentrations of cobalt as biological determinants of exposure to that element (see Section 2.6 for information on regulations and guidelines), but no

recommended biological exposure index (BEI) is listed for tungsten or cobalt–tungsten carbide hard metals (ACGIH 2007). The BEIs for cobalt are 15 μg/L in urine and 1 μg/L in blood, and are to be measured in end-of-shift, end-of-workweek samples.

The data used to develop the BEIs for cobalt included studies of hard-metal production and grinding operations as well as other industries (ACGIH 2001). ACGIH attributed the high inhomogeneity in the data relating exposure to cobalt and its compounds to urinary levels of cobalt "to differences in cobalt compounds used in the workplaces, to differences in the timing of urine collections, and to differences in analytical methods used in the studies." ACGIH concluded that good agreement exists between cobalt concentrations in ambient air and in urine based on data reported in five publications (Alexandersson and Lidums 1979, Angerer *et al.* 1985, Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Alexandersson 1988) from four studies, three of which were on hard-metal dust exposure (the Angerer *et al.* study looked at cobalt salts and powders). Based on the regression equations from these studies, ACGIH estimated that urinary cobalt levels ranging from 7 to 15 μg/L would most likely result from an air concentration of 20 $\mu g/m^3$ (which is the ACGIH TLV-TWA [see Section 2.6.2]). Similarly, the BEI for blood was based on data from four publications (Alexandersson and Lidums 1979, Angerer *et al.* 1985, Ichikawa *et al.* 1985, Alexandersson 1988) from three studies, two of which were of the hard-metal industry (data from a study of pottery painters was not used because ACGIH considered the variability in external exposure to be high). Based on the relationship between cobalt in air and in blood reported in these studies, ACGIH estimated that blood levels ranging from 1.1 to 2.3 μg/L would most likely result from an air concentration of 20 $\mu g/m^3$.

Significant correlations between cobalt air levels and cobalt levels in blood and/or urine have been found in several studies (Ichikawa *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994a, Scansetti *et al.* 1985). No correlation between air and urinary cobalt levels was found in two other studies by Scansetti *et al.* (1994, 1998), but the authors noted in the earlier study that the choice of a mid-week day for sampling and the potential contribution of skin (see Section 5.1.1 for information of dermal absorption of cobalt) or gastrointestinal absorption from the dirty working conditions could have presented a problem in determining an association, and in the later study they considered the data too scanty to find any significant association. Ichikawa *et al*. 1985 found significantly higher blood and urine levels for exposed workers than for office workers who were used as unexposed controls. They estimated that a cobalt exposure level of 100 $\mu g/m^3$ corresponded with 95% confidence interval concentrations for cobalt in blood of 0.57 to 0.79 μg/dL and in urine of 59 to 78 μg/L [creatinine values not reported.] The relationships between cobalt concentration in the breathing zones and those in blood and urine was linear and positive with significant correlations for blood ($r = 0.96$, $P < 0.001$) and urine ($r = 0.99$, $P < 0.001$). Sabbioni *et al.* (1994a) noted that good correlations existed between cobalt in air and cobalt in urine or blood, but that these correlations were more evident at lower concentrations than higher concentrations. Sabbioni *et al*. also reported significant correlations for cobalt with tungsten in urine ($r = 0.80$, $P < 0.001$), in hair ($r = 0.45$, $P < 0.01$), and in blood ($r = 0.14$, $P < 0.01$). Scansetti *et al.* (1985) reported significant correlations between cobalt in work-room air and urine for 10 different (out of

15 total) comparisons between exposure (for either a single day or the mean for a week) and urinary measurements (either beginning or end of shift). Comparisons for Monday ($r = 0.831$, $P < 0.01$), Wednesday ($r = 0.364$, $P < 0.05$), and Friday ($r = 0.351$, $P < 0.05$) between exposures for those days and end-of-shift urine levels were all significant. Similarly, Lison *et al.* (1994) compared the log of air cobalt concentrations with end-of-shift urinary cobalt levels for 10 hard-metals workers. Significant correlations were found for both Monday ($r = 0.80$, $P < 0.005$) and Friday ($r = 0.63$, $P < 0.03$).

Data also have been reported for tungsten in urine, which is another potential biomarker for exposure (Goldoni *et al*. 2004, Kraus *et al*. 2001, Sabbioni *et al*. 1994a, Della Torre *et al*. 1990). In an exposure assessment in a German hard-metal plant, Kraus *et al.* (2001) examined the variation in species of tungsten, and hence its bioavailability, across the different hard-metal production workshops (see Table 2-1 for tungsten exposure data). Powder processing resulted in exposure to tungsten metal, while tungsten carbide was identified during forming, pressing, and sintering. Production of tungsten carbide resulted in exposure to tungsten metal and oxide in addition to the carbide. Grinding processes involved exposures to tungstenate ($WO_4^{2-}$ or tungstate) for wet grinding and tungsten carbide and oxide for dry grinding. Tungsten bioavailability was reported to increase in the order: tungsten metal, tungsten carbide, tungstenate [the ranking of tungsten oxide was not provided]. The highest urinary concentrations for tungsten were found in workers in the grinding workshop (median = 70.9 μg/g creatinine), production of tungsten carbide (median = 48.9 μg/g creatinine) and heavy alloy production (median = 21.6 μg/g creatine).

Other biological media have been explored as potential indicators of hard-metal exposure, and cobalt or tungsten has been detected in other tissues in cobalt–tungsten carbide hard-metal workers. Nicolaou *et al.* (1987) and Sabbioni *et al.* (1994b) detected cobalt in whole blood, pubic hair, and toenails of cobalt–tungsten carbide hard-metal workers, and Kazantzis (1986) detected tungsten in the feces of 10 hard-metal production workers. Exhaled breath condensate (the fluid formed by cooling exhaled air), lung tissue, and mediastinal lymph node tissue also have been reported to contain cobalt or tungsten (Della Torre *et al.* 1990, Goldoni *et al.* 2004, Hillerdal and Hartung 1983, Mutti and Corradi 2006, Rizzato *et al.* 1992, Sabbioni *et al.* 1994a, Sjogren *et al.* 1980). In general, the authors of these studies proposed that cobalt (and tungsten in the Della Torre *et al.* study) in these media could be used to assess chronic or past exposures.

## 2.5 Environmental levels and general population exposure

The potential exists for exposure of people who live in the vicinity of hard-metal production or maintenance facilities to cobalt–tungsten carbide hard-metal dusts. While no exposure levels for the general public were found, this section describes studies that provide data for possible environmental contamination from the manufacture maintenance, or use of hard-metal products. In addition, family members of cobalt–tungsten carbide workers might be exposed from take-home exposures.

Abraham and Hunt (1995) investigated environmental contamination in the vicinity of a cemented tungsten carbide tool-grinding plant. At this facility, waste dusts generated from the grinding operation were swept from inside the building, out the backdoor, to

open ground at the rear of the plant, [but the use of air pollution control devices was not discussed]. Ventilation fans from inside the facility emitted dust to the outside air. Soil sampled from the rear of the factory contained cobalt levels as high as 12,780 mg/kg. Cobalt levels at the plot that had been used by local residents for gardening 20 m behind the building were 100 mg/kg in a cultivated area and 1,800 mg/kg in an uncultivated area. Concentrations ranged from 12 to 18 mg/kg in samples taken at 30 to 160 m from the building. The highest cobalt levels were over 1,700 times higher than the average value for cobalt in the soil in the United States, which the authors noted as 7.2 mg/kg. X-ray micro-analysis examination of the waste dust particles revealed that the individual particles were composites containing both cobalt and tungsten. The authors noted that studies had not been conducted on the local residents to assess exposure and that the scope of similar industrial/environmental contamination is not known.

A series of publications (Sheppard *et al.* 2006a,b,c, 2007a,b,c,d) reported elevated airborne tungsten and cobalt levels in Fallon, Nevada, where a hard-metal manufacturing facility is located. [See Appendix A for a description of a childhood-leukemia cluster that was identified in this area and prompted this and a number of other environmental investigations.] Airborne particulate samples were collected by 10 portable, high-volume particulate air samplers at two different times of the year (March to April and November) in Fallon and four nearby towns for comparison purposes (Sheppard *et al.* 2006a,b,c). The samples contained tungsten and cobalt (but not 17 other elements measured) air concentrations that the authors described as consistently and significantly ($P = 0.001$ to 0.002) higher in Fallon (tungsten = 0.1 to 40.9 ng/m$^3$; cobalt = 0.04 to 7.5 ng/m$^3$) than in the surrounding towns (tungsten = 0.02 to 0.16 ng/m$^3$; cobalt = 0.04 to 0.58 ng/m$^3$). Air modeling studies suggested that the elevated levels were not from natural sources. In follow-up studies, Sheppard *et al.* (2007c,d) reported higher concentrations of tungsten (12.5 times higher, $P < 0.001$) and cobalt (2.0 times higher, $P = 0.06$) in lichens (which the authors described as serving as a biomonitor for atmospheric chemical composition), but not in the rock substrates of the lichens from Fallon compared with four non-developed desert lands outside of Fallon, and they collected information on the spatial pattern of cobalt and tungsten in the surface dust, which peaked at 98 ppm for cobalt and 934 ppm for tungsten at a location in the vicinity of the hard-metals manufacturing facility located in Fallon. They also examined the temporal variability of cobalt and tungsten in the environment around Fallon through dendrochemistry (the study of elemental concentrations through time in tree rings). For Fallon, the authors reported that for the time period from 1989 to 1992, before the onset of the leukemia cases, median tree-ring tungsten levels were not statistically significantly different from the comparison towns; however, during the time period that centered on 1995 (the period right before the onset of the cluster), Fallon tree-ring tungsten levels started trending upward and were statistically higher than levels seen in the comparison towns (Sheppard *et al.* 2007a, 2008). During the following time periods (through 2002), the tungsten levels in Fallon continued trending upward and remained higher than comparison towns with significance levels at or near $P = 0.05$. The authors noted that cobalt levels in Fallon tree rings were consistently higher than comparison towns (statistically significant for the second and fourth of the four time periods; $P < 0.01$ or 0.02), but there was no significant increase through time within Fallon. Some of Sheppard and co-workers' conclusions have been questioned by other investigators, including Seiler *et al.* (2006), Sueker *et al.* (2006), and

Schell and Pardus (2008). The issues discussed in these studies are described in more detail in Appendix A.

A Finnish study reported tungsten levels ranging from 9.2 to 39 μg/g (depending on the particle size fraction of the dust) in urban street dust resulting from the use of tires with cobalt–tungsten carbide hard-metal studs (Peltola and Wikstrom 2006).

Take-home exposures (workers transporting contaminants home from the workplace) have been recognized as a potential source of exposure to the general public; especially to family members of workers in a variety of occupational settings, although there has been little systematic research on this subject (NIOSH 2002). It is reasonable to assume that the families of cobalt–tungsten carbide hard-metal workers could potentially be in contact with powders that remain on workers' skin and clothes after work. Indeed, in a study characterizing dermal exposure to cemented tungsten carbide workers from three U.S. production facilities, Day *et al*. (2008) discovered moderate levels of baseline skin contamination of cobalt, chromium, and nickel based on wipe samples taken at the start of the work shift. Wipe samples contained cobalt levels ranging from 0.8 to 410 μg for workers' hands and from 0.4 to 130 μg for workers' necks. The authors suggested that the contamination might have remained from the previous shift, suggesting the occurrence of take-home exposures.

## 2.6 Regulations and guidelines

While only one Federal regulation and one guideline have been developed specifically for cemented tungsten carbide [hard metal], numerous regulations and guidelines have been developed for cobalt and tungsten metals and compounds. These regulations and guidelines are presented in Sections 2.6.1 and 2.6.2.

### *2.6.1 Regulations*

**U.S. Environmental Protection Agency**

*Emergency Planning and Community Right-To-Know Act*

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

*Clean Water Act*

Effluent Guidelines:

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

**Occupational Safety and Health Administration**

Permissible Exposure Limit (PEL) for cemented tungsten carbide containing > 2% Co = 0.1 mg Co/$m^3$ (8-hour TWA)
PEL for cobalt metal, dust, and fume (as Co) = 0.1 mg/$m^3$
PEL for insoluble tungsten compounds (as W) = 5 mg/$m^3$
PEL for soluble tungsten compounds (as W) = 1 mg/$m^3$
Short-term exposure limit (STEL) for insoluble tungsten compounds (as W) = 10 mg/$m^3$
STEL for soluble tungsten compounds (as W) = 3 mg/$m^3$

### *2.6.2 Guidelines*

**American Conference of Governmental Industrial Hygienists**

Threshold Limit Value–Time-Weighted Average (TLV-TWA) limit for cobalt and inorganic cobalt compounds = 0.02 mg/$m^3$
TLV-TWA for tungsten metal and insoluble compounds = 5 mg/$m^3$
Threshold Limit Value–Short-Term Exposure Limit (TLV-STEL) for tungsten metal and insoluble compounds = 10 mg/$m^3$
TLV-STEL for soluble tungsten compounds = 3 mg/$m^3$
Biological Exposure Index (BEI)–cobalt in urine = 15 μg/L end of shift at end of workweek
BEI–cobalt in blood = 1 μg/L end of shift at end of workweek

**National Institute for Occupational Safety and Health**

Recommended exposure limit (REL) (10-hour TWA) for cemented tungsten carbide containing > 2% Co = 0.05 mg Co/$m^3$
REL for cobalt metal dust and fume (as Co) = 0.05 mg/$m^3$
Immediately dangerous to life and health (IDLH) level for cobalt metal dust and fume (as Co) = 20 mg/$m^3$
REL for tungsten and insoluble tungsten compounds (as W) = 5 mg/$m^3$
Short-Term Exposure Limit (STEL) for tungsten and insoluble tungsten compounds (as W) = 10 mg/$m^3$
REL soluble tungsten compounds (as W) = 1 mg/$m^3$
STEL soluble tungsten compounds (as W) = 3 mg/$m^3$

## 2.7 Summary

Cobalt–tungsten carbide hard metal is used primarily in cutting tools, to machine tempered steel, in rock drilling bits, and in a variety of tools. It is produced by preparing tungsten carbide from tungsten metal or tungsten oxide and carbon, adding a mixture of powdered cobalt metal and other compounds to produce cobalt–tungsten carbide powders, which are then pressed, shaped, sintered, and finished as hard-metal products. Total U.S. domestic production of hard-metal products was estimated at 5,527 metric tons [6,080 tons] in 2004, and the USGS estimated that 6,610 metric tons [7,286 tons] of tungsten and 792 metric tons [873 tons] of cobalt were used in the production of cemented carbides in the United States in 2007. Workers potentially are exposed to respirable dusts at many points during the manufacturing process, and dermal exposures also have been demonstrated. Exposure can be assessed by measuring ambient air

concentrations of cobalt or tungsten or by biological monitoring, including measurements of cobalt or tungsten in urine, blood, tissues, or exhaled air. Exposure generally is highest among workers handling hard metal in powder form before or during the sintering process (Step 2). Exposure also can occur during the grinding or sharpening of hard-metal blades (Step 3) and from other processes. At facilities that use hard metals, exposure is generally highest for individuals who are involved in the maintenance, sharpening, and grinding of tools. Historically, exposure levels from production have decreased over time, possibly as a result of improved industrial hygiene in hard-metal producing factories. The potential exists for general-population exposures to cobalt–tungsten carbide hard-metal powders for persons living near facilities that manufacture or process hard metal or hard-metal products. There is one OSHA regulation specific to cemented tungsten carbide (a synonym for hard metals), although there are numerous other regulations for cobalt and tungsten metals and compounds. Similarly, there is one guideline for cemented tungsten carbide and numerous guidelines for cobalt and tungsten metals and compounds.

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# 3 Human Cancer Studies

An IARC Working Group reviewed the carcinogenicity of cobalt in hard metals in 2003, updating its previous review of cobalt and cobalt compounds (IARC 1991) with a new monograph (IARC 2006). IARC concluded that there was limited evidence of carcinogenicity of cobalt in hard metals in humans, based on epidemiological studies showing an increased risk of lung cancer among workers exposed to hard-metal dust containing cobalt and tungsten carbide with evidence of an elevation of risk with increasing exposure and taking into account potential confounding by smoking and occupational carcinogens.

For this review, searches for studies concerning the risk of cancer in humans exposed to hard metals used the following keywords: "hard-metal, cancer, epidemiology," "carbide, cancer, epidemiology," and "cobalt, cancer, epidemiology."

Because all the human studies evaluating the carcinogenicity of cobalt–tungsten carbide hard-metals were conducted in hard-metal manufacturing factories, a brief description of the process is included in this section. [As noted in Section 2, the terms "hard metals" and "cobalt–tungsten carbide" are generally synonymous for the products of this industry.] This section discusses four publications of cancer mortality in hard-metal manufacturing workers, followed by a discussion of their findings and a summary of the evidence from human cancer studies. The studies are summarized in Table 3-1.

No adequate epidemiological studies have been conducted that evaluated the relationship between childhood leukemia and exposure to cobalt–tungsten carbide hard metals and powders. As mentioned in Section 2 and Appendix A, a cluster of childhood leukemia was identified in Fallon, Nevada, which is also the site of a hard-metal facility. A cross-sectional case comparison study was conducted (Rubin *et al.* 2007); but no relationship was found between leukemia occurrence and urinary tungsten levels. However, the study did not assess exposure to tungsten carbide, cobalt, or hard metals (see Appendix A.2 for more details on this study).

## 3.1 Hard-metal manufacturing process

While exposure to cobalt can occur through a multiplicity of routes (diet, smoking, water, soil, or air and of course through occupational exposure), exposure to hard metals occurs primarily in hard-metal producing factories or factories in which hard-metal tools are finished or sharpened by grinding.

There are three main steps in the industrial process used in the manufacture of hard-metal tools (see also Section 2.2.1 and Figure 2-1):

**Step 1:** the production of the cobalt and tungsten carbide powders;
**Step 2:** the mixing of the powders, drying, pressing, presintering, shaping of the presintered hard metal, and sintering; and
**Step 3:** the finishing of the sintered products.

Depending on the industrial site, all three steps or any of these steps are concomitant, but only the last two steps always give rise to "hard-metal exposures." In the first step, workers may be exposed to only cobalt dust or to only tungsten carbide dust.

The primary organ site relevant to potential carcinogenicity of exposure to powders and hard metals of cobalt–tungsten carbide is the lung, through inhalation.

## 3.2 Cohort studies

This section discusses four cohort studies of cobalt–tungsten carbide hard-metal manufacturing workers.

### *3.2.1 Hogstedt and Alexandersson (1990)*

#### *Population and follow-up*

Hogstedt and Alexandersson (1990) studied all male workers in the workforce (N = 3,163) of three hard-metal producing factories. Factory A (1,191 workers) was established in Stockholm (which had high lung cancer rates) in the 1930s, whereas Factory B (1,869 workers) was established in a rural area in the early 1950s, and Factory C (103 subjects) was established in the 1940s. Mortality was followed from 1951 to 1982; workers who reached age 80 were excluded from further follow-up because the national statistics ended at 80 years of age. (The number of person-years was not reported.) Foreign-born workers and those who emigrated from Sweden were excluded. Vital status and death certificates were obtained from the Swedish central statistical office, and causes of death were coded according to *International Classification of Diseases, Revision 8* (ICD-8). Expected numbers of deaths by cause were based on national death rates, and Standardized Mortality Ratios (SMRs) were calculated using standard life-table methods.

#### *Exposure assessment*

Exposure was assessed retrospectively using measurements from the 1950s and from the 1970s, and expert knowledge of working conditions and how they evolved over the relevant decades. Workers were classified into the following exposure groups: group 0, unexposed; group 1, intermittent exposure in hard-metal producing workshops; group 2, continuous exposure in hard-metal producing workshops, but without direct involvement in production; group 3, production of hard-metal tools; and group 4, hard-metal production with exposure to powdered cobalt. The specific steps in hard-metal production performed by workers in each group were not described; however, it appears that workers in group 3 were exposed to dust from sintered hard-metal tools (Step 3), whereas workers in group 4 were exposed to unsintered hard-metal dust (Step 2). For statistical analysis, groups 1 and 2 were combined into a low-exposure group, and groups 3 and 4 into a high-exposure group. Each worker's duration of exposure was computed. For the 9 workers assigned to more than one exposure group, the duration of exposure in the highest-exposure group was used. No workers in Factory B were assigned to group 4, and almost all workers in group 4 were from Factory A. Based on retrospective estimation, eight-hour cobalt exposure in groups 1 and 2 was always below 5 $\mu g/m^3$; exposure in group 3 ranged from 20 to 30 $\mu g/m^3$ from 1940 to 1960 and 10 to 20 $\mu g/m^3$ since 1960;

and exposure in group 4 ranged from 500 to 11,000 μg/m$^3$ in the 1940s, 60 to 600 μg/m$^3$ in the 1950s, 60 to 400 μg/m$^3$ in the 1960s, and 60 to 140 μg/m$^3$ in the 1970s.

*Results*

The SMR for all causes was 0.96 (95% confidence interval [CI] = 0.85 to 1.07, 292 deaths). Overall, non-significant excesses were observed for lung cancer (SMR = 1.34, 95% CI = 0.77 to 2.13, 17 deaths), pancreatic cancer (SMR = 1.66, 95% CI = 0.71 to 3.27, 8 deaths), prostate cancer (SMR = 1.62, 95% CI = 0.77 to 2.97, 10 deaths), and leukemia (SMR = 2.31, 95% CI = 0.92 to 4.77, 7 deaths). For each tumor site, the authors calculated SMRs for low- and high-exposed workers, low- and high-exposed workers stratified by latency and/or exposure time, and for workers at the three different factories. SMRs for lung cancer were similar in low- (1.31, 11 vs. 8.4 expected deaths) and high-exposure groups (1.39, 6 deaths vs. 4.3 expected), and were higher when the analysis was restricted to workers whose time since first exposure was greater than 20 years (SMR = 2.02, [95% CI = 0.54 to 5.2], 4 deaths for the low-exposure group; SMR = 2.30, [95% CI = 0.62 to 5.9], 4 deaths for the high-exposure group). The lung-cancer SMRs increased again when the analysis was further restricted to workers with duration of exposure greater than 10 years and > 20 years latency (SMR = 2.27, [95% CI = 0.54 to 6.6], 3 deaths for the low-exposure group; SMR = 3.33, [95% CI = 0.90 to 8.5], 4 deaths for the high-exposure group). When the analysis combined all exposed workers with time since first exposure greater than 20 years and duration of exposure greater than 10 years the excess lung-cancer mortality became statistically significant (SMR = 2.78, 95% CI = 1.11 to 5.72, 7 deaths). SMRs were the highest among workers in Factory A (1.71, 12 deaths vs. 7 expected) and were less than one among workers in Factory B and were 1.07 for factory C (based on 1 observed death). In both the total cohort and Factory A, where exposures were highest, SMRs were somewhat higher among workers with exposure times from 1 to 4 years than workers with 5 or more years of exposure, though these differences were not statistically significant. In addition, 4 of the 292 deaths observed in this cohort resulted from pulmonary fibrosis, which may represent pneumoconiosis associated with exposure to hard-metal dust.

With respect to leukemia, a higher SMR was found in the low-exposure group (2.94, 6 observed vs. 2.0 expected deaths) compared with the high-exposure group (1.01, 1 observed vs. 1.0 expected death). A statistically significant SMR for leukemia was found with 1 to 4 years of exposure (SMR = 7.69, 95% CI = 2.49 to 17.95, 5 deaths); however, the SMR for workers at Factory A with greater than 5 years of exposure was 1.21, 95% CI = 0.03 to 6.77, 1 death). A similar pattern, that is higher SMRs among workers with shorter exposure times than longer exposure time, was observed among the entire cohort. SMRs for leukemia were not calculated for different latency periods.

The SMR for prostate cancer was somewhat higher among the high-exposure group (SMR = 2.05, 4 observed vs. 1.9 expected deaths) than the low-exposure group (SMR =1.42, 6 observed vs. 4.2 expected deaths) and among workers with longer periods (> 5 years) of exposure; however, the risks were not higher among workers with longer latency, and no significant SMRs were reported. No consistent exposure-response

patterns were found for tumors at other sites. [Subgroup analyses were limited by small numbers of observed and expected deaths.]

*Strengths and limitations*

[Given the small size of the hard-metal production industry, this study examined a relatively large cohort, with an overall expected lung cancer mortality of 12.7 deaths. However, in absolute terms, the sample size was small, and when analysis was restricted to workers with estimated eight-hour cobalt exposure greater than 5 $\mu g/m^3$, expected lung-cancer mortality was only 4.3 deaths. Given these small numbers, the power to detect a statistically significant excess was very small. Despite the limited statistical power associated with the subgroup with > 20 years latency and > 10 years employment duration, the elevated lung cancer SMR associated with this subgroup was statistically significant. Another potential problem was due to the use of national death rates; the largest and oldest factory (Factory A), which accounted for almost all workers in exposure group 4, was located in the Stockholm area, where the lung cancer rate was 30% above the national rate. Thus, the expected numbers of deaths for the high-exposure group likely were underestimated, and the SMRs thus overestimated. The authors also noted that most of the low-exposure groups were in Factory B, which was in the countryside, and the use of national statistics would provide expected values that are too high. [The choice of reference death rates is a general problem with SMRs, which can be solved by conducting analyses within the cohort.]

[It is not clear from this paper whether complete job histories were available, but it seems unlikely, given that the authors reported a 15% misclassification rate when 100 randomly selected workers were reclassified by the same consultant who made the initial classification.] Potential confounding was not treated in any detail. A survey of this workforce in the late 1970s showed their smoking habits not to differ from those of the Swedish population, suggesting that confounding from smoking was not likely. Exposure to other potential occupational carcinogens (such as asbestos or nickel) was not discussed.

Hogstedt and Alexandersson commented that the excess of leukemia, primarily in Factory A (Stockholm) was difficult to explain. Excesses for cirrhosis of the liver and circulatory organ diseases were also observed in the temporary employees in Stockholm. The authors commented that temporary employees might have alcohol problems, poor eating habits, and high consumption of tobacco, and might also have several high occupational exposures in the various jobs. These workers often are given the least attractive jobs with poor working conditions.

### *3.2.2 Lasfargues* et al. *(1994)*

*Population and follow-up:*

Lasfargues *et al.* (1994) followed the mortality of all male workers (N = 709) at a hard-metal producing plant in central France from 1956 to 1990 (12,027 person-years). This cohort also was included in the cohort described by Moulin *et al.* (1998) (Section 3.2.3). Vital status was obtained from registry offices at the birthplaces of subjects born in France and at the central French registry for foreign-born workers. Workers whose vital

status could not be determined were considered lost to follow-up when they left the factory. Causes of death were obtained from general practitioners and hospitals and were coded according to ICD-9. Expected numbers of deaths by cause were based on national death rates, and SMRs were calculated using standard life-table methods. Data on smoking habits (never-smokers, ex-smokers, and current smokers) were obtained from medical records and interviews with still active workers and were available for 81% of the workers.

*Exposure assessment*

Each worker was classified into one of the following exposure groups: group 1, unexposed (mainly clerical workers); group 2, low exposure (maintenance workers outside the hard-metal production workshops and hard-metal finishing workers using protective devices [Step 3]); group 3, medium exposure (hard-metal finishing workers not using protective devices [Step 3], workers machining unsintered materials with protection [Step 2 before sintering], and workers at the oven [Step 2]); and group 4, high exposure (workers involved in powder mixing, pressing, and machining of unsintered materials without protection [Step 2 production]). Eight-hour exposures to cobalt were measured in this plant in 1983; levels for the groups defined above were as follows: group 2, less than 10 $\mu g/m^3$; group 3, 15 to 40 $\mu g/m^3$; and group 4, more than 50 $\mu g/m^3$. As no detailed job histories were available, each worker was assigned to one exposure group. Nonclerical workers hired before 1974 for which no work-history information was available were assigned to group 3. Duration of exposure was approximated by duration of employment in the plant.

*Results*

The SMR for all causes was 1.05 (95% CI = 0.82 to 1.31, 75 deaths). There was a non-significant excess of all malignant neoplasms (SMR = 1.25, 95% CI = 0.81 to 1.83, 26 deaths), due mainly to a significant excess of lung cancer (SMR = 2.13, 95% CI = 1.02 to 3.93, 10 deaths) and a non-significant excess in leukemia (SMR = 3.09, 95% CI = 0.37 to 11.14, 2 deaths). The lung cancer excess was due mainly to a large excess in the high-exposure group (SMR = 5.03, 95% CI = 1.85 to 10.95, 6 deaths). The SMR for lung cancer among workers in the high-exposure group whose time since first employment was 10 to 19 years was 6.79 (95% CI = 1.40 to 19.85, number of deaths not provided). In combined analysis of smoking and exposure to hard metals, elevated SMRs for lung cancer were found among never smokers with high exposure (SMR = 6.71, 2 deaths), current smokers with medium (SMR = 9.20, 3 deaths) or high exposure (SMR = 15.14, 3 deaths), and unknown for smoking status and high exposure (SMR = 4.24, 1 death), [but these analyses were based on small numbers of cases]. Lung cancer mortality did not increase with duration of employment or time since employment. No excess in mortality was found for respiratory disease (non-malignant).

*Strengths and limitations*

[For this small cohort of hard-metal workers, overall expected lung cancer mortality was 4.69 deaths. When the analysis was restricted to workers with an estimated daily cobalt exposure above 15 $\mu g/m^3$, the expected number of lung cancer deaths was only 3.27. Given these small numbers, the power to detect any significant excess was very small.

Nonetheless, a significantly elevated SMR for lung cancer was observed in the high-exposure group. Complete job histories were not available, and duration of employment may be a poor proxy for duration of exposure. The power for detecting a trend was very small given the cohort size. Potential confounding was treated in some detail for smoking, as some information on smoking habits was available for 9 of 10 workers who died of lung cancer and 81% of the cohort members. The smoking habits of the cohort did not differ from those of the French population, and two workers in the high-exposure group who died of lung cancer were nonsmokers so that confounding by smoking is unlikely. Exposure to other potential occupational carcinogens was not discussed.]

### *3.2.3 Moulin* et al*. (1998)*

*Population and follow-up*

Moulin *et al*. (1998) studied the mortality of the workforce (N = 7,459; 5,777 men and 1,682 women) of all 10 French hard-metal producing plants (most of which were located in eastern France). This cohort included the cohorts studied by Lasfargues *et al*. (1994) (Section 3.2.2) and Wild *et al*. (2000) (Section 3.2.4). A nested case-control study of lung-cancer mortality also was conducted. The mortality of this population was followed from 1968 to 1991 (114,834 person-years, 88,738 for men and 26,096 for women). Vital status was obtained from registry offices at the birthplaces of workers born in France and at the central French registry for foreign-born workers. Workers whose vital status could not be determined (1,131 workers or approximately 15% of the subjects) were considered lost to follow-up and were censored on the date when they left the factory; the authors noted that 875 of the workers lost to follow-up "were born abroad and could not be traced after leaving the factory." Causes of death, coded according to ICD-8 until 1975 and ICD-9 thereafter, were obtained from the central registry. Expected numbers of death by cause were based on national death rates, and SMRs were calculated using standard life-table methods. Information on smoking habits (never, former, or current smokers) was obtained from interviewing colleagues (70.5% cases and 51.3% controls), relatives (11.5% cases and 9.11% controls) and the subjects themselves (0% cases and 18.8% controls), and was summarized as ever vs. never smoker.

In the nested case-control study, 3 controls for each worker who died of lung cancer were sampled from the cohort, matched on sex and date of birth within 6 months. Job histories were obtained for most cases (61 of 63) and controls (180 of 184), and smoking (ever vs. never) for 82% of cases and 79% of controls. All exposure indices were lagged 10 years to account for disease latency.

*Exposure assessment.*

An industry-specific job-exposure matrix was created through consensus of nine experts (epidemiologists, occupational physicians, industrial hygienists, and industry representatives) using a Delphi method. Their assessment was based on plant visits, historical description of the industrial processes, and interviews with former workers. This assessment was blind with respect to existing exposure measurements (for details see Moulin *et al.* 1997). The matrix included 320 combinations of factory, job, and time period, to which were assigned "semiquantitative" estimates of exposure to sintered (Step 3) and unsintered hard-metal dust (Step 2), cobalt alone (in the cobalt powder production

workshops), and tungsten carbide alone (in the tungsten carbide production workshops) (Step 1). Specifically, the combinations were assigned exposure intensity codes on a scale of 0 to 9 (where 0 = no exposure and 9 = highest exposure) and exposure frequency scores (less than 10%, 10% to 50%, and over 50% of working time). The matrix also included "yes/no" assessments of exposure to other potential carcinogens, including PAHs, asbestos, silica, nitrosamines, benzene, arsenic compounds, cadmium compounds, and certain chromium and nickel compounds.

It was not possible to assign a "typical exposure" value to the semiquantitative coding of the matrix because there were no systematic exposure measurements. However, there were exposure measurements available from 1971 to 1994 for certain workplaces of certain factories. For these samples, cobalt semiquantitative exposure codes from the job-exposure matrix were significantly correlated with the log-transformed measured cobalt concentrations. The assessment was blind to these measurements.

*Results*

The SMR for all causes was 0.93 (95% CI = 0.87 to 1.01, 684 deaths). There was a non-significant excess of all malignant neoplasms (SMR = 1.07, 95% CI = 0.94 to 1.21, 247 deaths) due to a borderline significant excess of lung cancer (SMR = 1.30, 95% CI = 1.00 to 1.66, 63 deaths) and non-significant excesses of malignant neoplasms of the upper digestive tract (SMR = 1.20, 95% CI = 0.77 to 1.79, 24 deaths), esophagus (SMR = 1.22, 95% CI = 0.73 to 1.90, 19 deaths), and pleura (SMR = 1.98, 95% CI = 0.41 to 5.79, 3 deaths).

In the nested case-control study, the odds ratio (OR) for lung-cancer mortality following simultaneous exposure to cobalt and tungsten carbide at exposure intensity levels of 2 or higher (vs. 0 or 1) was 1.93 (95% CI = 1.03 to 3.62, 26 cases) after adjustment for other cobalt exposure (exposure to cobalt alone or with agents other than tungsten carbide). The OR increased significantly with duration of exposure (decades) and cumulative exposure (quartiles based on intensity level times duration, not weighted by frequency), and non-significant trends ($P = 0.08$) were observed for exposure level and frequency-weighted cumulative dose. Significant ORs were observed for the highest quartiles for cumulative exposure vs. the lowest exposure group, reaching 4.13 (95% CI = 1.49 to 11.47, 23 cases) for unweighted cumulative doses and 2.73 (95% CI = 1.02 to 7.26, 19 cases) for frequency-weighted cumulative dose. In the subset of individuals with known smoking habits (50 cases and 143 controls), adjustment for smoking or other potential confounders did not change the trends and had little influence on the ORs. No excess mortality was found for non-malignant respiratory diseases though three workers died from pneumoconiosis. The SMR for emphysema and chronic bronchitis was 0.21.

*Strengths and limitations*

[The major strengths of this study were its relatively large size, its relatively good control of potential confounders (both smoking and exposure to other potential occupational carcinogens), and its semiquantitative exposure scale that allowed detection of exposure-response relationships. Its main weaknesses were the heterogeneity of the industrial processes among the various sites and the difficulty of retrospective exposure estimation.

Although the basic industrial process of production of hard metals is similar at different facilities, the exposure levels can be quite different, as observed in the wide range of cobalt exposure measurements associated with each semiquantitative code. For levels 2 through 5, based on the personal samples, the ratio of the 97.5 to the 2.5 percentile ranged from 108 to 1,206. Therefore, it would be misleading to identify a "typical dose" associated with an exposure level. There is also potential for confounding from other agents, especially in the largest cohort included in this study (described in Wild *et al.* 2000), which included workers exposed to a wide range of other production processes, some of which involved other cobalt exposures and exposure to other known carcinogens (see Section 3.3). In the present paper these other exposures were summarized in the binary item "other cobalt exposures."]

### *3.2.4 Wild* et al*. (2000)*

#### *Population and follow-up*

Wild *et al.* (2000) followed the mortality of the workforce of a hard-metal producing plant in eastern France from 1968 to mid 1992 (N = 2,860; 2,216 men and 644 women). This cohort was included in the cohort described by Moulin *et al*. (1998) (Section 3.2.3). Vital status was obtained from registry offices at the birthplaces of workers born in France and at the central French registry for foreign-born workers. Workers whose vital status could not be determined were considered lost to follow-up when they left the factory. Follow-up continued until either the date of death or the person's 85$^{th}$ birthday [the reason for selecting this age to end follow-up was not stated]. A total of 40,542 person-years was accumulated for men and 11,960 for women. Causes of death, coded according to ICD-8 until 1975 and ICD-9 thereafter, were obtained from the central registry. Expected numbers of deaths by cause were based on regional death rates, and SMRs were calculated using standard life-table methods. Exposure to smoking was obtained from occupation health department records, though limited information was available about smoking prior to 1978. The authors stated that this information was "sketchy" until 1978, and thus was reassessed by a volunteer group of former workers.

#### *Exposure assessment*

The plant was established in the late 1940s. Hard-metal production co-existed with other production processes involving cobalt, mostly based on powder metallurgy; these included production of magnets, stainless steel, stellite, other sintered alloys of iron, nickel, copper, and tin, and cobalt powder and tungsten carbide powder. Workshops were categorized as non-exposed, hard-metal production before sintering, hard-metal production after sintering, production of other sintered alloys, foundries, and powder production. Detailed individual job histories were available, including jobs performed within given workshops. The job-exposure matrix developed for the industry-wide study by Moulin *et al.* (1998) was used to compute individual exposures and durations. All exposure indices were lagged 10 years to account for disease latency.

#### *Results*

The SMR for all causes was 0.98 (95% CI = 0.88 to 1.10, 331 deaths) for men and 1.26 (95% CI = 0.98 to 1.60, 68 deaths) for women. [Because of the small numbers of

observed and expected cases among females (22 vs. 17.49 expected from all malignances and 1 vs. 0.84 expected from lung cancer, only the results from males are described in this background document.] Overall, there was a non-significant excess of all malignant neoplasms among males (SMR = 1.08, 95% CI = 0.90 to 1.30, 118 deaths), due mainly to a significant excess of lung cancer (SMR = 1.70, 95% CI = 1.24 to 2.26, 46 deaths), and non-significant excesses of malignant neoplasms of the upper digestive tract (SMR = 1.53, 95% CI = 0.84 to 2.57, 14 deaths), esophagus (SMR = 1.35, 95% CI = 0.62 to 2.57, 9 deaths), and pleura (SMR = 2.44, 95% CI = 0.27 to 8.81, 2 deaths). No significant excesses for mortality from non-malignant respiratory diseases were observed.

*By workshop:* For hard-metal production (without distinguishing between exposure to sintered or unsintered hard metal) for males for lung cancer, the SMR was 1.93 (95% CI = 1.05 to 3.23, 14 deaths). Higher SMRs were found for workers ever employed in pre-sintering hard-metal production (SMR = 2.42, 95% CI = 1.10 to 4.59, 9 deaths) or only employed in pre-sintering hard-metal production (SMR = 2.91, 95% CI = 1.06 to 6.34, 6 deaths). Excess mortality was relatively small among ever-employed (SMR = 1.28, 95% CI = 0.41 to 2.98, 5 deaths) and only-employed (SMR = 1.13 (95% CI = 0.31 to 2.89, 3 deaths) workers in post-sintering hard-metal production, SMRs were non-significantly elevated for several other workshops (foundries, other alloys, and cobalt powder production), but significantly elevated for the maintenance workshop (SMR = 2.56, 95% CI = 1.28 to 4.59, 11 deaths). Although maintenance work was not specific to any industrial process, the job-exposure matrix identified most maintenance jobs as involving intermittent (low-frequency) high exposures to hard-metal dusts, including the jobs of 10 of the 11 maintenance workers who died of lung cancer.

*By job-exposure matrix:* For all hard-metal exposure levels of 2 or higher (combined) for males for lung cancer, the SMR was significantly elevated (SMR = 2.02, 95% CI = 1.32 to 2.96, 26 deaths). Significant SMRs (~2-fold) were also found for the highest exposure quartiles for cumulative dose (both unweighted and frequency weighted); non-significantly increased SMRs were found for the highest category of exposure duration (SMR = 2.65, 95% CI = 0.85 to 6.17, 5 deaths) and exposure score (SMR = 2.80, 95% CI = 0.76 to 7.16, 4 deaths). The SMRs increased with exposure duration ($P = 0.07$), but tests for trends for cumulative exposure were not significant in models that adjusted for smoking and exposure to any "IARC carcinogen" (defined as PAHs, silica, nickel compounds, chromium compounds, or cobalt [without tungsten]).

The SMR for subjects exposed to any IARC carcinogen was significantly elevated (SMR = 2.05, 95% CI = 1.34 to 3.00, 26 deaths). In an internal estimation of relative risk (RR) by Poisson regression, adjusted for smoking and exposure to any IARC carcinogen, the RR increased significantly with duration of exposure to unsintered hard-metal dust at an exposure level of 2 or higher. No increased RR was found for exposure to sintered hard-metal dose (yes vs. no) in this model.

### *Strengths and limitations*

[Although this cohort was smaller than that of Moulin *et al.* (1998), in which it was included, hard-metal exposure was more precisely defined than in the industry-wide study as the exposure was more homogeneous. The availability of job histories (and thus

exposure estimates) for all cohort members allowed for a more powerful internal comparison of risk. The main limitations of this study were the lack of direct measurements of exposure to hard-metal dust and co-exposure to several other production processes (involving other cobalt exposures and exposure to other IARC carcinogens), so that limited confounding of the internal dose-response relationship is possible.]

## 3.3 Discussion

The populations in the three French studies overlapped to some extent, as the cohort followed by Moulin *et al*. from 1968 to 1991 included most of the populations followed by Lasfargues *et al*. from 1956 to 1989 and Wild *et al.* from 1968 to 1992. The latter two cohorts were, however, completely independent. [The Lasfargues *et al.* (1994) cohort was small and was completely included in the study by Moulin *et al.* (1998), which had two more years of follow-up and improved exposure assessment. Although the cohort studied by Wild *et al.* (2000) was also included in the report by Moulin *et al.*, the Wild *et al.* paper added information through a more detailed exposure-response analysis and improved control for confounding.]

### *3.3.1 Confounding*

In all four studies, the smoking habits of the cohort were similar to those of the reference population. [In the studies by Hogstedt and Alexandersson (1990) and Lasfargues *et al.* (1994) smoking was controlled for only indirectly.] Moulin *et al.* suggested the possibility of an interaction between exposure to hard-metal dust and smoking (based on a non-significant interaction in the subset of workers with known smoking habits in the case-control study). However, both Lasfargues *et al.* and Wild *et al.* observed a small excess of lung cancer even among nonsmoking workers exposed to hard-metal dust. Neither Hogstedt and Alexandersson nor Lasfargues *et al.* discussed exposure to other occupational carcinogens. Wild *et al*. considered exposure to a number of other potential carcinogens, and their internal RR analysis, which showed significantly increased risk with increasing duration of exposure to hard-metal dust, was adjusted for both smoking and exposure to other carcinogens (grouped as "any IARC carcinogen"). Moreover, the SMR in this study was significantly elevated in a subcohort not exposed to other carcinogens (workers employed only in pre-sintering hard-metal production). Moulin *et al*. also considered other potential carcinogens, and the analysis of the nested case-control study, which showed a significantly increased OR with increased cumulative hard-metal exposure, was adjusted for both smoking and other cobalt exposure. [The lack of excess non-malignant respiratory disease deaths, especially chronic obstructive lung disease or emphysema, and other smoking-related cancers, suggests limited potential for confounding by smoking in these studies. Both the Moulin *et al.* and Wild *et al.* studies used internal analyses (via nested case-control analysis in the former and Poisson regression in the latter), which are usually less susceptible to confounding relevant to comparisons with external referent populations.]

### *3.3.2 Exposure assessment and exposure-response relationships*

[As in most occupational studies, a major limitation of these studies is the potential for error in measuring exposure to cobalt–tungsten carbide powders and hard-metal powders.

None of the studies had quantitative exposure estimates for individual workers. The exposure assessments in the Swedish study (Hogstedt and Alexandersson 1990) and the small French study (Lasfargues *et al.* 1994) are relatively crude, and workers were classified into either two or four exposure categories. More comprehensive exposure assessments were performed in the studies by Moulin *et al.* (1998) and Wild *et al.* (2000). These studies used the same job-exposure matrix, based on plant visits, historical records, and interviews, and calculated semi-quantitative estimates of exposure to hard-metal dust (both sintered and unsintered), cobalt alone, and tungsten carbide alone. The semi-quantitative exposure scores from the job-exposure matrix were significantly correlated with the available measurements of cobalt in air, but exposures were not uniform within groups (see Section 3.2.3). The sample sizes within exposure groups are also small, which reduces the precision of the estimated exposure level, particularly in groups 6 and 7. In most cases, such random errors in estimating exposure lead to attenuation of observed exposure-response relationships toward the null value. Exposure misclassification also decreases the power to detect a positive exposure-response relationship. Another major limitation is that the exposure assessment was semi-quantitative rather than quantitative and, thus, it is not possible to estimate the risk per unit of exposure. Semi-quantitative exposure assessments also limit the ability to separate the effects of cobalt and tungsten carbide.]

[In the studies by Hogstedt and Alexandersson (1990) and Lasfargues *et al.* (1994), exposure assessment was relatively crude. Although these cohorts were too small to have any power to detect a significant trend, the largest SMRs were reported for the highest exposure categories. For the larger cohorts of Moulin *et al*. and Wild *et al.*, significant exposure-response trends were observed; however, because the former study included the cohort of the latter study, these observations cannot be considered to be independent.] Moulin *et al*. reported that the ORs in the nested case-control study increased significantly with increasing unweighted cumulative exposure (OR = 4.13, 95% CI = 1.49 to 11.5, 23 cases in the highest exposure quartile). This exposure-response relationship was based on a semiquantitative exposure code for hard-metal exposure obtained from an expert-based, job-exposure matrix. Although these semiquantitative ratings were significantly correlated ($P = 0.015$ for long-duration personal or area samples and $P < 0.0001$ for short-duration area sampling) with cobalt measurements in the French hard-metal industry, very few long-duration personal exposure measurements were available for exposure intensity levels over 5 (on the scale from 0 to 9), and the range of measured exposures within each level was very broad. Wild *et al.* found significantly increased risks among workers in the highest exposure quartiles for exposure score and cumulative exposure (both unweighted and frequency weighted). In internal analyses that adjusted for smoking and exposure to other carcinogens, the RR increased significantly with duration of exposure to unsintered hard-metal dust. [A strength of the Moulin *et al.* and Wild *et al.* studies is that they focused on internal comparisons (via nested case-control analysis in the former and Poisson regression in the latter). As mentioned above, internal analyses are usually more informative in assessing causality than comparisons to external referent populations.]

### *3.3.3 Human cancer studies evaluating other exposures to cobalt and tungsten*

The IARC 2006 monograph evaluated two studies on exposure to cobalt not related to cobalt–tungsten carbide hard powders and hard metals. A study by Mur *et al*. (1987) found an excess of lung cancer in a cobalt production workshop, which was not confirmed in a follow-up study by Moulin *et al.* (1993b). (Excesses of lung cancer mortality were observed among maintenance workers; however, the IARC working group noted that this might be explained by other carcinogenic exposures such as smoking or asbestos). Tuchsen (1996) studied a cohort of Danish porcelain workers exposed to aluminate spinel and/or cobalt silicate at two factories. Although a significantly increased risk of lung cancer was observed in exposed workers compared with the Danish population, lung cancer risk was also increased in a reference group of non-exposed workers at one of the factories; the relative risk ratio between exposed and reference group was 1.2 (95% CI = 0.4 to 3.8). [No adequate database exists for the evaluation of potential carcinogenicity of tungsten to humans.]

In addition, two studies of the hard-metal industry also evaluated exposure to cobalt that did not include tungsten carbide. Moulin *et al*. (1998) reported a two-fold increased risk for lung cancer mortality for exposure to cobalt alone or simultaneously with agents other than tungsten carbide. Wild *et al.* (2000) observed a slight excess of lung cancer mortality (2 deaths) among workers in the cobalt powder production workshop.

## 3.4 Summary

Workers in the cobalt–tungsten carbide powders and hard-metal (hereafter called hard metals) industry are exposed to either presintered or sintered hard-metal particles. Four cohort studies (although not independent) were identified that evaluated exposure to hard metals and cancer mortality. These studies included a (1) a cohort study of Swedish workers at three hard-metals facilities (Hogstedt and Alexandersson 1990), (2) a small cohort of French hard-metal manufacturing workers (Lasfargues *et al.* 1994), (3) a multi-plant cohort study of workers at 10 hard-metal producing factories in France, which also included a nested case-control analysis (Moulin *et al.* 1998), and (4) a cohort study of the largest factory of the multi-plant French study (Wild *et al.* 2000). The multi-plant study also included workers studied by Lasfargues *et al.* All of the studies attempted to evaluate exposure-response relationships, although the exposure assessments by Hogstedt and Alexandersson and Lasfargues *et al.* were crude. Both Wild *et al.* and Moulin *et al.* attempted to control for smoking and/or other occupational exposure, and the Lasfargues *et al.* (1994) study provided data that showed that the study population differed little in smoking habits from a national sample of French men.

All four studies reported an increased lung cancer risk, with significantly increased lung cancer mortality either in the whole cohort or among workers with higher or longer exposure, or longer latency. Hogstedt and Alexandersson found significant excess lung cancer mortality in a subgroup of long-latency, long-exposure–duration workers, and Lasfargues *et al.* found a five-fold significantly elevated SMR in their high-exposure group. Moulin *et al.* found an overall increase in lung cancer mortality of borderline statistical significance and significantly increased risk for exposure levels higher than level 2 compared with the lowest level. In the nested case-control study, the risk of lung

cancer increased significantly with duration of exposure ($P = 0.03$) and cumulative dose (unweighted) ($P = 0.01$) and non-significantly increased with exposure level ($P = 0.08$) and cumulative dose (frequency weighted) ($P = 0.08$). Adjustment for smoking or known or suspected carcinogens did not change the ORs. Wild *et al.* found significantly elevated lung cancer SMRs among all workers and workers ever employed in pre-sintering workshops, and among the highest exposure category (exposure score, unweighted cumulative exposure, weighted cumulative exposure) to hard-metal dusts. In models controlling for smoking and exposure to any "IARC carcinogen" (PAHs, silica, nickel compounds, chromium compounds, or cobalt without tungsten), the test for trends was of borderline significance for exposure duration and was not significant for exposure level or cumulative dose. In analyses that evaluated exposure to unsintered hard metals, a significantly increased trend for duration of exposure was found in models that controlled for smoking and exposure to any "IARC carcinogen." No increased risk for exposure to sintered metals was found in this model.

Hogstedt and Alexandersson was the only study to evaluate risks for tumors sites other than lung in more details; specifically, they evaluated risks by exposure groups, exposure duration, and individual factory. They reported a significant excess risk for leukemia among workers employed at one of the factories and exposed for less than 5 years, but not among longer exposed workers. A non-significant excess of leukemia was found among the small cohort study of French workers (Lasfargues *et al.*), but not among the larger studies (Moulin *et al.*, Wild *et al.*). Non-significant excesses of cancer of the esophagus (Lasfargues *et al*., Moulin *et al.*, Wild *et al.*), upper GI (Moulin *et al.*, Wild *et al*.), and pleura (Moulin *et al.,* Wild *et al.*) were found in the overlapping French studies.

**Table 3-1. Cohort studies of cancer mortality in cobalt–tungsten carbide hard-metal manufacturing workers**

| Reference | Study design and follow-up | Population and methods | Exposure | Effect: SMR, OR, or RR | Comments |
|---|---|---|---|---|---|
| Hogstedt and Alexandersson 1990<br>Sweden | Historical mortality cohort study<br>1951–1982 | All male workers at 3 hard-metal producing factories who had worked at least 1 yr in hard-metal production (N = 3,163)<br>Person-years not reported<br>Causes of death from national registry<br>National death rates | Workers were divided into two exposure groups:<br>Low exposure in production workshops without direct involvement in production (Groups 1 and 2) (< 5 μg/m$^3$)<br>High exposure in hard-metal production, either in machining of hard-metal products (Group 3) or in pre-sintering hard-metal production processes (Group 4)<br>Group 3: 10–30 μg/m$^3$; Group 4: 10–11,000 μg/m$^3$ | SMR (95% CI); number of deaths<br>Overall 0.96 (0.85–1.07); 292<br>*Cancers with excess mortality*<br>(all exposed men [1951 to 1982])<br>leukemia 2.31 (0.92–4.77); 7<br>prostate 1.62 (0.77–2.97); 10<br>pancreas 1.66 (0.71–3.27); 8<br>*Lung cancer*<br>total cohort 1.34 (0.77–2.13); 17<br>≥ 10-yr exposure and > 20-yr latency<br>2.78 (1.11–5.72); 7<br>> 20-yr exposure level and latency<br>low 2.02 [0.54–5.2]; 4<br>high 2.35 [0.064–6.02]; 4<br>10-yr exposure duration and exposure level<br>low 2.27 [0.54–6.6]; 3<br>high 3.33 [0.90–8.5]; 4 | [Some exposure misclassification likely]<br>High mortality for several causes among short-term (< 5 years) workers<br>Factory A was the oldest factory, with the highest exposures<br>No adjustment for smoking, but a survey of this workforce suggested that the number of smokers among active workers was close to national average |
| Lasfargues *et al.* 1994<br>France | Historical mortality cohort study<br>1956–1989 | All male workers of a hard-metal producing factory who had worked at least 1 yr at this site (N = 709)<br>12,027 person-years<br>Causes of death from general practitioners and hospital records<br>National death rates | Time since first employment and duration of employment<br>Exposure to hard-metal dust in four groups (cobalt exposure, μg/m$^3$):<br>1. unexposed<br>2. low (maintenance) (< 10)<br>3. medium (sintered) (15–40) | SMR (95% CI); number of deaths<br>*Overall mortality* 1.05 (0.82–1.31); 75<br>*Cancers with excess mortality*<br>Entire cohort<br>leukemia 3.09 (0.37–11.14); 2<br>esophagus 1.90 (0.39–5.55); 3<br>lung 2.13 (1.02–3.93); 10<br>No subgroup analysis for cancers other than lung (numbers of cases were small) | High mortality from suicide (SMR = 3.66, 13 deaths), especially in high-exposure groups<br>[Some exposure misclassification likely]<br>Numbers of smokers among active workers close to national average<br>Lung cancer excess among |

| Reference | Study design and follow-up | Population and methods | Exposure | Effect: SMR, OR, or RR | Comments |
|---|---|---|---|---|---|
| | | Smoking from medical records and personal interviews | 4. high (unsintered) (> 50)<br><br>No complete work histories | *Lung Cancer*<br>Exposure category<br>no 1.52 (0.04–8.48); 1<br>low 0.00 (0.00–5.18); 0<br>medium 1.44 (0.30–4.21); 3<br>high 5.03 (1.85–10.95); 6<br>Exposure duration (yr)<br>1–9 3.39 (1.36–6.98); 7<br>10–19 1.23 (0.03–6.84); 1<br>≥ 20 2.52 (0.06–14.02); 1<br>Time since first employment (yr)<br>1–9 1.86 (0.05–10.39); 1<br>10–19 3.65 (1.19–8.53); 5<br>≥ 20 2.17 (0.45–6.34); 3 | high-exposure nonsmokers (SMR = 6.71; 2 deaths) |
| Moulin *et al.* 1998<br><br>France | Historical mortality cohort study and nested case-control study<br><br>1968–1991 | *Cohort study*<br>All workers at 10 hard-metal producing factories who had worked at least 3 months at any site (N = 7,459; 5,777 men and 1,682 women)<br><br>114,834 person-years (88,738 for men and 26,096 for women)<br><br>Causes of death from national registry<br><br>National death rates<br><br>*Case-control study*<br>Cases: 61<br>Controls: 180<br><br>For each lung cancer | An industry-specific job-exposure matrix was used to assign semiquantitative exposure intensity codes (0 = no exposure to 9 = highest exposure) and frequency codes to sintered and unsintered hard-metal dust<br><br>Yes/no assessment of exposure to several other potential carcinogens based on historical description of the industrial processes<br><br>The semiquantitative exposure intensity levels significantly correlated with available measurements of cobalt | *Cohort Study (both sexes)*<br>SMR (95% CI); number of deaths<br>overall 0.93 (0.87–1.01); 684<br>upper GI 1.20 (0.77–1.79); 24<br>esophagus 1.22 (0.73–1.90); 19<br>pleura 1.98 (0.41–5.79); 3<br>lung 1.30 (1.00–1.66); 63<br><br>*Nested case-control study: lung cancer*<br>OR (95% CI); cases/controls<br>Exposure level<br>2+ vs. 0–1 1.93 (1.03–3.62); 35/81<br>0–1 1.0; 26/99<br>2–3 3.37 (1.19–9.56); 8/12<br>4–5 1.54 (0.76–3.12); 19/55<br>6–9 2.79 (0.96–8.10); 8/14<br>test for trend, $P = 0.08$<br><br>Exposure duration (yrs) (levels 2+) | No increased SMR for any other cause of death<br><br>*Unweighted cumulative dose* (same value for occasional and fulltime exposure, thus favoring peak exposures)<br><br>[The exposure measurements were insufficient to quantitatively characterize the exposure levels]<br><br>[Some exposure misclassification was likely, both from the job-exposure matrix and from the actual job histories]<br><br>The smoking OR was smaller than expected, due to a large percentage (20%) of nonsmokers among workers |

| Reference | Study design and follow-up | Population and methods | Exposure | Effect: SMR, OR, or RR | Comments |
|---|---|---|---|---|---|
| | | case, 3 controls were sampled from the cohort, matched by sex and year of birth<br>Job histories and smoking obtained from administrative and medical records and interviews with colleagues | Exposure of cases and controls was based on 10-yr-lagged maximal exposure intensity, duration of exposure intensity, duration of exposure, and frequency-weighted and unweighted cumulative doses | no exposure 1.0; 26/99<br>≤ 10 1.61 (0.78–3.34); 19/52<br>10–20 2.77 (1.12–6.82); 12/20<br>> 20 2.03 (0.49–8.51); 4/9<br>test for trend, $P = 0.03$<br><u>Unweighted cumulative dose</u><br>< 32 1.0; 6/46<br>32–142 2.64 (0.93–7.47); 16/43<br>143–299 2.59 (0.88–7.6); 16/45<br>> 299 4.13 (1.49–11.47); 23/46<br>test for trend, $P = 0.01$<br><u>Frequency-weighted cumulative dose</u><br>< 4 1.0; 8/45<br>4–27 2.28 (0.86–6.06); 20/45<br>27–164 1.85 (0.66–5.20); 14/45<br>> 164 2.73 (1.02–7.26); 19/45<br>Test for trend, $P = 0.08$ | who died of lung cancer. [This points to a possible misclassification of smoking]<br>OR for other cobalt exposure (cobalt alone or with other agents other than tungsten carbide)<br>Levels 2–9/ vs. 0–1<br>2.21 (0.99–4.90); 15/30 |
| Wild *et al.* 2000<br>France | Historical mortality cohort study<br>1968–1992 | All workers at the largest hard-metal producing factory from Moulin *et al.* (1998) who had worked at least 3 months at this site (N = 2,860; 2,216 men and 644 women)<br>40,542 person-years for men, 11,960 for women<br>Causes of death from national registry | The job-exposure matrix of Moulin *et al.* (1997) was used.<br>Exposure to hard-metal dust was expressed as the maximal hard-metal exposure level, duration of exposure to cobalt–tungsten carbide hard metals, and frequency-weighted and unweighted cumulative exposure.<br>Exposure to other potential carcinogens was | SMR (95% CI); number of deaths<br>*Overall mortality*<br>men 0.98 (0.88–1.10); 331<br>women 1.26 (0.98–1.60); 68<br>*Cancers with excess mortality, males*<br>upper GI tract 1.53 (0.84–2.57); 14<br>esophagus 1.35 (0.62–2.57); 9<br>pleura 2.44 (0.27–8.81); 2<br>lung 1.70 (1.24–2.26); 46<br>*Lung Cancer*<br>By workshop (ever employed)<br>pre-sintering 2.42 (1.10–4.59); 9 | Overall mortality close to expected (SMR = 1.02, 399 deaths)<br>No increased SMR for any other cause of death<br>No quantitative estimates of hard-metal exposure were available<br>[The availability of full job histories and the participation of the former industrial physician probably limited exposure misclassification]<br>The number of smokers in |

| Reference | Study design and follow-up | Population and methods | Exposure | Effect: SMR, OR, or RR | Comments |
|---|---|---|---|---|---|
| | | Regional death rates<br>Complete job histories from company records<br>Smoking obtained from medical records and validated by a group of former workers | summarized as yes/no.<br>The data allowed analysis by workshops: non-exposed workshops, pre-sintering hard-metal production, post-sintering hard-metal production, and other exposed. | post-sintering 1.28 (0.41–2.98); 5<br>By job-exposure matrix<br>exposure score (levels)<br>0–1 1.41 (0.86–2.17); 20<br>2–3 2.10 (0.84–4.33); 7<br>4–5 1.85 (1.03–3.04); 15<br>≥ 6 2.80 (0.76–7.16); 4<br>≥ 2 2.02 (1.32–2.96); 26<br>Test for trend, $P = 0.17$<br>exposure duration (yr)<br>none 1.41 (0.86–2.17); 20<br>< 10 1.57 (0.78–2.81); 11<br>11–19 2.51 (1.20–4.61); 10<br>> 20 2.65 (0.85–6.17); 5<br>Test for trend, $P = 0.07$<br>unweighted cumulative dose<br>1 1.17 (0.50–2.30); 8<br>2 1.66 (0.83–2.97); 11<br>3 1.61 (0.80–2.88); 11<br>4 2.36 (1.35–3.83); 16<br>Test for trend, $P = 0.23$<br>weighted cumulative dose<br>1 1.33 (0.61–2.53); 9<br>2 1.62 (0.81–2.89); 11<br>3 1.78 (0.92–3.10); 12<br>4 2.06 (1.1 3–3.46); 14<br>Test for trend, $P = 0.37$<br>Poisson regression, adjusted for smoking and exposure to other potential carcinogens<br>RR (95% CI) for hard metal<br>unsintered 1.43 (1.03–1.98)<br>sintered 0.75 (0.37–1.53) | the cohort was close to the national average in 1980. The SMR among nonsmokers was larger than expected (SMR = 1.35, 7 deaths)<br>[The thorough search for information on smoking habits probably limited smoking misclassification]<br>Test for trend adjusted for smoking and exposure to any IARC carcinogen |

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# 4 Studies of Cancer in Experimental Animals

No studies of the carcinogenicity of cobalt–tungsten carbide powders or hard metals in experimental animals were identified. Studies of the carcinogenicity of cobalt and cobalt compounds in experimental animals are summarized in Section 5.4.1.

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# 5 Other Relevant Data

This section discusses mechanistic data and other relevant information needed to understand the toxicity and potential carcinogenicity of cobalt–tungsten carbide powders and hard metals. It includes information on absorption, distribution, metabolism, and excretion (Section 5.1), toxicity studies (Section 5.2), genotoxicity studies (Section 5.3), a brief review of the carcinogenicity, toxicity, and genotoxicity of cobalt or tungsten individually (Section 5.4), mechanistic studies (Section 5.5), and an overall summary (Section 5.6).

## 5.1 Absorption, distribution, metabolism, and excretion

### *5.1.1 Humans*

Humans are exposed to cobalt–tungsten carbide hard-metal particles, mainly in occupational settings during hard-metal production, through inhalation and dermal contact. Numerous biomonitoring studies have detected cobalt in the urine of workers exposed to cobalt–tungsten carbide powders and hard metals, providing further evidence for the absorption of cobalt from cobalt–tungsten carbide hard metals in humans (Gallorini *et al.* 1994, Linnainmaa and Kiilunen 1997, Lison *et al.* 1994, Nicolaou *et al.* 1987, Sabbioni *et al.* 1994b, Scansetti *et al.* 1994, Scansetti *et al.* 1998) (see Sections 2.3 and 2.4). [Although the manufacture of cobalt–tungsten carbide hard metals begins with cobalt powder as one starting material, the published studies do not report exposures in sufficient detail to identify workers exposed solely to cobalt as compared with those exposed to cobalt as a constituent of cobalt–tungsten carbide hard metals.] Gallorini *et al.* (1994) detected both inorganic and organic forms of cobalt (about twice as much organic as inorganic) in the urine of hard-metal workers. Several studies (Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994a) have reported a relationship between cobalt concentrations in the urine and air (see Section 2.4 for details). However, Scansetti *et al.* (1994, 1998) did not find a correlation with levels of cobalt in ambient air and urinary cobalt concentrations among Italian cobalt tungsten carbide hard-metal workers, which the authors attributed to substantial skin contact. In one of those studies (Scansetti *et al.* 1994) the absorption of cobalt through the skin was demonstrated. The urinary concentration of cobalt increased by an order of magnitude in subjects who each held one of their hands in a box filled with either freshly mixed cobalt–tungsten carbide powder (about 5% to 15% cobalt and 85% to 95% tungsten carbide) or waste dry powder.

After absorption, cobalt is distributed but does not accumulate in any specific organ except for the lung after inhalation of insoluble particles (IARC 2006). However, cobalt or tungsten has been detected in other tissues in cobalt–tungsten carbide hard-metal workers, including pubic hair, toenails, and mediastinal lymph node tissue (Della Torre *et al.* 1990, Goldoni *et al.* 2004, Hillerdal and Hartung 1983, Mutti and Corradi 2006, Nicolaou *et al.* 1987, Rizzato *et al.* 1992, Sabbioni *et al.* 1994a, Sjogren *et al.* 1980).

The particles present in the occupational setting usually are of respirable size [≤ 10 μm], indicating that they potentially are deposited throughout the respiratory tract, including in

the alveoli. Studies in humans indicate that when cobalt–tungsten carbide hard-metal particles are deposited in the lung, cobalt metal is rapidly solubilized, cleared from the lung, distributed in the body, and excreted in urine; whereas, tungsten carbide particles persist longer in lung tissue (reviewed by IARC 2006, Lison 1996, Lison *et al.* 1996). Particles containing cobalt and tungsten carbide have been found in the lungs of exposed workers (see Section 2.4). Tungsten and other particles (including cobalt, silicon, aluminum, and titanium) were detected in human lung tissue from 3 workers employed in the metal- and tool-cutting and grinding industries and suspected to have occupationally induced lung disease (Stettler *et al.* 1983). Rizzato *et al.* (1986) reported high concentrations of tungsten and cobalt, along with tantalum, in lung specimens from an Italian man who had worked for 13 years grinding hard metals to sharpen tools. Rüttner *et al.* (1987) analyzed dust in lung tissue from lung biopsies (N = 7) or whole lungs from autopsies (N = 9) of 16 metal grinders exposed to hard metals for 5 to 44 years and found small or trace amounts of cobalt, tungsten, or both metals in 14 of 16 samples. Schwarz *et al.* (1998) evaluated 14 workers exposed to dust containing hard metals and aluminum oxide. Microchemical analysis of transbronchial biopsies in five workers showed a high lung burden of metal particles. Tungsten was found in all five workers and was associated with tantalum, titanium, aluminum, and iron. Cobalt was found in one worker.

Apostoli *et al.* (1994) reported a diphasic excretion of cobalt by workers exposed to cobalt powders. Peak elimination occurred about 2 to 4 hours after exposure and decreased over the following days. Torra *et al.* (2005) also reported a multiphasic pattern for cobalt excretion by hard-metal workers with a rapid first stage of elimination (half-life of 21 hours) and a slower second phase (half-life of 9 days). Kazantzis (1986) also detected tungsten in the feces of 10 hard-metal production workers.

### *5.1.2 Experimental animals*

Similar to humans, when cobalt–tungsten carbide hard-metal particles are deposited in the lung of experimental animals, the cobalt metal is rapidly solubilized, cleared from the lung, distributed in the body, and excreted in urine; whereas, tungsten carbide particles persist longer in the lung tissue (reviewed by Lison 1996). Lasfargues *et al*. (1992) administered 1 mg/100 g body weight (b.w.) of pure cobalt metal powder or 16.67 mg/100 g b.w. of cobalt–tungsten carbide (equivalent to 1 mg/100 g b.w. of cobalt) to female rats by intratracheal instillation. These authors reported that rats administered cobalt–tungsten carbide excreted significantly greater amounts of cobalt in the urine at 24 hours compared with rats administered pure cobalt. The authors suggested that cobalt has a greater bioavailability when combined with tungsten carbide. Lison and Lauwerys (1994) administered equivalent doses of cobalt metal alone or mixed with tungsten carbide by intratracheal instillation and monitored urinary excretion of cobalt at 6, 12, 24, and 48 hours. Twenty-four–hour urine samples also were collected from some animals one week after treatment. Rats exposed to cobalt alone initially excreted cobalt at a much lower rate than rats exposed to cobalt–tungsten carbide powder; however, after 48 hours, both groups had excreted almost identical amounts. On day 7, no significant difference in cobalt excretion rates was seen between the two groups. The authors also measured cobalt concentrations in the lung. After day 1, lung concentrations of cobalt were two times higher in rats administered cobalt as compared with cobalt–tungsten carbide;

however, after day 7, the mean concentration of the metal retained in the lung had decreased significantly to almost the same level in both groups.

### *5.1.3* In vitro *studies*

*In vitro* experiments with cobalt–tungsten carbide dust (71.4% cobalt and 24% tungsten), labeled with radioisotopes ($^{60}$Co and $^{187}$W) have characterized the interaction of cobalt and tungsten with human blood and homogenized lung tissue (Edel *et al.* 1990). Cobalt was highly soluble, especially in the lung cytosol and plasma. Three biochemical pools were identified for cobalt. More than half (56%) of the dissolved cobalt was associated with low-molecular–weight components and represented the diffusible and highly mobile fraction. About 34% was associated with proteins with molecular weights of 70,000 to 80,000 daltons, and 8% was associated with high-molecular-weight components. The authors reported that tungsten had a very low solubility and low affinity for plasma or tissue proteins, thus, they concluded that the small amounts of solubilized tungsten are highly mobile. The authors also concluded that the ability of cobalt and tungsten to dissolve in body fluids is consistent with the transport of the metals from the lung to other tissues such as pubic hair and toenails, and their presence in the urine of exposed individuals (see above and Section 2.4).

Lison and Lauwerys (1992) investigated the solubilization of cobalt from different powders in murine macrophages *in vitro* and determined that the solubilization of cobalt powders increased by a factor of 4 in the presence of tungsten, which is consistent with the *in vivo* findings reported by Lasfargues *et al*. (1992). Lison *et al.* (1995) also reported increased solubility of cobalt in the presence of tungsten carbide.

Stopford *et al.* (2003) compared the solubility of selected cobalt compounds (including presintered and sintered cobalt–tungsten carbide) in artificial human tissue fluids (interstitial fluid, lysosomal fluid, alveolar fluid, synovial fluid, gastric juice, and intestinal juice) and human serum (pH = 1.5 for gastric juice, 4.5 to 5.0 for lysosomal fluid, and 7.0 to 7.4 for all other fluids). Four separate extraction times from 2 to 72 hours were used. Results were expressed as a percentage of available cobalt to allow comparison between different compounds and extraction fluids. The solubilities of presintered samples ranged from 2.6% in alveolar fluid to 25.9% in lysosomal fluid and differed little from sintered samples, which had solubilities ranging from 3.6% in alveolar fluid to 26.7% in lysosomal fluid.

Lombaert *et al.* (2004) investigated the solubilization of cobalt(II) ions from metallic cobalt, cobalt–tungsten carbide, and cobalt chloride in cell-free medium. Metallic cobalt was 77.5% solubilized after 15 minutes, and complete solubilization was achieved after 24 hours. The cobalt from the cobalt–tungsten carbide mixture was 74.5% solubilized after 15 minutes, and no further change was observed after 24 hours. Cobalt chloride was completely solubilized within 1 minute.

### *5.1.4 Cobalt metals, cobalt compounds, and tungsten metal and tungsten compounds*

Information on the biological fate of cobalt metal and cobalt compounds and of tungsten metal and tungsten compounds other than the carbide supports the conclusion that cobalt

and tungsten are absorbed after either ingestion, inhalation, or dermal exposure (Elinder and Friberg 1986, Kazantzis 1986, Linnainmaa and Kiilunen 1997). Studies in workers exposed to cobalt suggest that the absorption rate of various cobalt compounds is probably dependent on their solubility in biological fluids and in the alveolar macrophages. Exposure to less soluble cobalt compounds was associated with lower absorption rates (and probably a longer retention time in the lung) than absorption rates after exposure to more soluble cobalt-containing particles (such as hard-metal particles) (Lison *et al.* 1994, Lison and Lauwerys 1994, as cited in IARC 2006). Both elements distribute primarily to the lung after inhalation and to the liver after ingestion. Tungsten also distributes to bone (Leggett 1997). Persson *et al.* (2003) reported that intranasal administration of $^{57}Co^{2+}$ in rats resulted in uptake of the metal in the olfactory mucosa with subsequent transport to the olfactory bulbs of the brain. Low levels of cobalt migrated into the interior of the bulbs and the anterior parts of the olfactory cortex. Limited evidence is available for metabolism of cobalt to organically complexed forms *in vivo* (Gallorini *et al.* 1994), but no corresponding information on metabolism of tungsten was found. Both elements are excreted primarily in the urine (Kazantzis 1986, Lison *et al.* 1994). The biological half-life of cobalt is independent of exposure route. Most is eliminated within days, but about 10% has a biological half-life of 2 to 15 years (Elinder and Friberg 1986).

## 5.2 Toxicity

This section reviews the primary toxic effects of hard-metal particles in humans and experimental animals, as well as the enhanced cytotoxicity produced by the interaction of cobalt–tungsten carbide particles. The most common toxic effects occur at the site of contact or deposition (skin and respiratory system). These effects include contact dermatitis and bronchial asthma, which likely result from immunological sensitization to cobalt, and hard-metal lung disease (IARC 2006). Occupational inhalation exposure to cobalt–tungsten carbide hard-metal dust has been associated with the occurrence of hard-metal disease, a giant-cell interstitial pneumonia that can develop into pulmonary fibrosis, with a potentially fatal outcome. Extrapulmonary effects reported in humans include memory loss, heart disease, and Goodpasture's syndrome. [Goodpasture's syndrome is an autoimmune disorder that affects the lungs and kidneys. It is rapidly progressive and usually fatal.] Systemic effects are not believed to be caused by the metallic particles themselves, but may occur from the release of cobalt ions into the blood or indirectly from lung damage (IARC 2006).

### *5.2.1 Humans*

#### *Contact dermatitis*

Allergic contact dermatitis of the face, ears, and neck has been reported in hard-metal workers (Dooms-Goossens *et al.* 1986). The allergic contact dermatitis associated with sensitization to cobalt or its compounds is a Type IV, or delayed type, hypersensitivity reaction (Nordberg 1994). Fischer and Rystedt (1985) reported that 10% of 776 workers examined at a hard-metal factory had hand eczema while 15% had irritant reactions. The authors noted that hand eczema has a more protracted course and is more inflammatory than irritant reactions. Of more than 1,000 workers who had left the industry during the

previous 10 years, 87 had hand eczema; although, the cumulative incidence of hand eczema for those 10 years was estimated at 17%. More than half of the cases of hand eczema, and about 67% of the cases of irritant reactions occurred during the first year of work. The highest risk was associated with grinding activities where exposure to cutting oils and fluids was high. Linnainmaa *et al.* (1997) investigated respiratory symptoms and dermatoses among grinders and brazers of hard-metal and stellite blades. This study included 108 workers involved in the manufacture or maintenance of tools, 116 saw filers in the mechanical wood-processing industry, and two reference groups. The cobalt-exposed workers did not have a higher incidence of hand dermatoses or symptoms of metal allergy than the unexposed workers. Sjögren *et al.* (1980) reported concurrent contact eczema and interstitial pulmonary disease in four case reports of workers exposed to hard metals during grinding operations. In each case, the eczema first appeared within a few months of starting work in the wet-grinding area.

### *Respiratory effects*

Chronic exposure to mineral dust in the workplace can result in chronic bronchitis, asthma, or emphysema. Specific respiratory effects from cobalt–tungsten carbide exposure include bronchial asthma and hard-metal lung disease, characterized by interstitial lung fibrosis. Although both diseases are considered relatively uncommon (Meyer-Bisch *et al.* 1989, Sprince *et al.* 1988), occupational asthma as a result of cobalt exposure has a greater frequency of occurrence than hard-metal disease (Cugell 1998, Nemery *et al.* 2001).

Occupational asthma can occur as a result of cobalt sensitivity in workers exposed to hard-metal dust (Shirakawa *et al.* 1989). It has been hypothesized that cobalt combines with protein to produce a hapten allergen eliciting a type I hypersensitivity reaction through the production of IgE antibodies (Skirakawa *et al.* 1989, Sjögren *et al.* 1980). Shirakawa *et al.* (1988) measured specific IgE antibodies to cobalt-conjugated human serum albumin in sera of 6 out of 12 hard-metal workers with a confirmed respiratory sensitivity to cobalt. In a follow-up study (Shirakawa *et al.* 1989), 8 workers with occupational asthma were shown to be sensitive to cobalt exposure, but only 4 were positive for IgE antibodies specific to cobalt exposure. The authors noted that hard-metal asthma may be a complex syndrome involving several types of sensitivity reactions, including an IgE-mediated mechanism in some people.

Some authors use the term “hard-metal lung disease” to refer to all respiratory diseases resulting from exposure to hard-metal dust, while others restrict the term to parenchymal manifestations in hard-metal workers, exclusive of obstructive disorders (Kelleher *et al.* 2000). Further, the medical terminology used for the interstitial lung pathology observed as a result of hard-metal and cobalt dust exposures has been described as “confusing” (IARC 2006, Nemery *et al.* 2001). The earlier literature usually referred to the disease as a pneumoconiosis; however, hard-metal disease differs from other mineral pneumoconioses in that it is due to individual susceptibility, rather than from a cumulative dust burden in the lungs (Nemery *et al.* 2001, Sjögren *et al.* 1980). Hypersensitivity to cobalt alone can lead to contact dermatitis and hypersensitivity pneumonitis, which can progress with continued exposures to interstitial fibrosis in the

lungs (Cugell 1998). However, unlike most other occupationally derived airway irritants and allergens, inhalation exposure to hard metals can lead to irreversible effects on the lung parenchyma, resulting in interstitial fibrosis and giant-cell pneumonia (Nemery *et al.* 2001). Giant-cell interstitial pneumonia is unique to hard-metal disease and considered pathognomonic (IARC 2006, Ohori *et al.* 1989).

Recent experimental and epidemiological evidence suggests that this disease is caused by the interaction of cobalt metal with tungsten carbide particles (reviewed by Lison *et al.* 1996). Hard-metal lung disease also has been described in workers exposed to cobalt from diamond-coated polishing disks, and some older studies suggested that cobalt (and not tungsten carbide) caused the respiratory effects observed in hard-metal workers (Davison *et al.* 1983, Harding 1950, Sprince *et al.* 1984). However, only rare cases of interstitial disease have been reported in workers exposed to cobalt alone, and there are many more workers exposed to cobalt alone than hard metals. Linna *et al.* (2003) found no cases of hard-metal disease or fibrosing alveolitis among 110 cobalt production workers exposed to cobalt but not to hard metals. Lison and coworkers (Lison 1996, Lison *et al.* 1996) concluded in reviews of the epidemiological literature that interstitial lung disease occurs only among hard-metal and diamond workers and suggested a role for simultaneous inhalation of other compounds such as tungsten carbide or diamond dust in addition to cobalt. The occurrence of both fibrosing alveolitis and lung cancer in hard-metal workers has been suggested to be related mechanistically, conceivably involving oxidative damage and/or inflammatory events (IARC 2006). In addition, Bouros *et al.* (2002) reported than an excessive relative risk of lung cancer has been found in patients with pulmonary fibrosis compared with the general population; however, the pathogenesis of lung cancer in these patients is unclear.

Although the pathogenesis of giant-cell interstitial pneumonia is unknown (Chiappino 1994, Nemery *et al.* 2001), involvement of the immune system has been proposed (Ruediger 2000). Moriyama *et al.* (2007) investigated the distribution of inhaled hard-metal particles and reactive inflammatory cells in lung tissues from 17 patients with hard-metal lung disease. Tungsten and cobalt (especially tungsten) had accumulated in the centrilobular fibrotic lesions of the patients but not in the controls. Further, $CD163^+$ macrophages co-localized with tungsten particles within the centrilobular fibrotic lesions, and $CD8^+$ lymphocytes also were distributed in and around the fibrotic lesions. [$CD8^+$ lymphocytes are a subset of T lymphocytes that can release cytotoxic factors such as reactive oxygen species. $CD163^+$ macrophages can engulf foreign particles.] The authors noted that their data provided evidence that both $CD163^+$ macrophages and $CD8^+$ lymphocytes have a role in the pathogenesis of fibrotic alveolar lesions. Frost *et al.* (1993) suggested an autoimmune mechanism for giant-cell interstitial pneumonia based on recurrence of the disease in a transplanted lung despite the absence of any further industrial exposure. Hahtola *et al.* (2000) described a case of allergic alveolitis accompanied by rheumatoid arthritis, another disease resulting from an abnormal immune response, in a woman whose trade was hard-metal sharpening. Other case reports have demonstrated an association between hard-metal disease and the expression of the cytokines transforming growth factor-beta 1 (Corrin *et al.* 1994) and tumor necrosis factor alpha (Rolfe *et al.* 1992) in lung cells. Potolicchio *et al.* (1997) reported a strong genetic association between hard-metal disease and the presence of a glutamate

residue at position 69 of the HLA-DP [MHC II antigen] molecule. In a later publication, Potolicchio *et al.* (1999) demonstrated that HLA-DP but not HLA-DR could bind cobalt *in vitro*, which they suggested could be a possible explanation for this genetic association with hard-metal disease.

#### *Extrarespiratory effects*

Memory loss has been reported and studied in patients diagnosed with hard-metal disease (Jordan *et al.* 1990, 1993, 1997). In one study (reported in Jordan *et al.* 1990, 1993), 12 former tungsten carbide workers who had complained of memory loss were compared with 26 healthy, unexposed adults matched for sex, age, race, and education. All subjects were administered the Wechsler Memory Scale-Revised (WMS-R), the Peterson Word Triad, and Squire's Television Title Recognition Tests. The test groups were found to have significantly lower verbal memory ($P < 0.001$) and attention ($P < 0.01$) scores, but no differences in visual-spatial memory. It was noted by the authors that exposures to mixed solvents by the patients with hard-metal disease was a potentially confounding factor. In a second study (Jordan *et al*. 1997), exposure to mixed solvents was controlled for by including a group with exposure to mixed solvents but no hard-metal exposures. Memory tests were administered for a range of functions: attention, short-term, delayed, and remote verbal and visual memory. Both groups exhibited memory deficits compared with unexposed controls on tests of verbal memory and attention. The authors acknowledged that the evidence for independent effects of exposure to hard metals on memory over exposure to solvents alone was inconclusive. However, when the authors selected for more closely matched groups, hard-metal workers had memory deficits greater than those attributable to solvent exposure alone.

Cobalt is cardiotoxic, and there is conflicting evidence that industrial exposure to cobalt can cause cardiomyopathy (IARC 2006). Horowitz *et al.* (1988) found that cobalt exposure was associated with adverse effects on ventricular function among hard-metal workers. Hogstedt and Alexandersson (1990) reported an increased risk (border line significance) of death from ischemic heart disease among hard-metal workers in the high-exposure group who were exposed for at least 10 years; however, no excess mortality from ischemic heart disease was found in the studies of French hard-metal workers (Moulin *et al.* 1998, Wild *et al.* 2000, Lasfargues *et al.* 1994).

Lechleitner *et al.* (1993) reported a case of Goodpasture's syndrome in a 26-year-old man who had worked in a metallurgical plant processing hard metals for three years. The patient presented with fever and dyspnea. High amounts of tungsten, but no cobalt, were detected in granular inclusions contained in alveolar macrophages. The authors concluded that although a causative role of hard-metal exposure and the development of Goodpature's syndrome could not be proved conclusively, the case did illustrate the potential complex interrelations among autoimmune disease, immune defects, and exposure to substances with possible antigenic properties.

### *5.2.2 Animal models of hard-metal toxicity*

Rats exposed to hard-metal particles developed some features of hard-metal disease, particularly alveolitis and fibrosis, in some, but not all, studies. However, Nemery and

Hoet (2000) reported that multinucleated giant cells, which they identified as the most characteristic feature of hard-metal lung disease, have not been observed in any animal studies. The effects of hard metals on inflammation and fibrosis in the lung of experimental animals are summarized below.

Schepers (1955a,b) investigated the effects of intratracheal instillation or inhalation of cobalt metal alone or mixed with tungsten carbide in guinea-pigs [age and strain not reported]. Acute chemical pneumonitis with diffuse eosinophilic infiltration and obliterative bronchiolitis occurred in a dose-related manner following intratracheal instillation of 10 to 50 mg of cobalt. A single instance of bronchial adenomatosis was reported after 12 months in the high-dose group. Intratracheal instillation of 150 mg of tungsten carbide and cobalt in a 10:1 ratio resulted in a transient inflammatory reaction with residual papillary hypertrophy of bronchial mucosa and peribronchial and periarterial fibrosis in the vicinity of the retained particles. Inhalation of tungsten carbide and cobalt in a 3:1 ratio caused severe acute inflammation followed by focal pneumonitis and residual bronchial epithelial hyperplasia and metaplasia.

Kaplun and Mezencewa (1960)[1] investigated the toxicity of the individual components of hard metals and the mixtures in rats [age and strain not reported in English abstract] following intratracheal instillation. They reported that the lung toxicity induced by cobalt metal particles was exacerbated by the simultaneous addition of tungsten or titanium. The pathological changes observed in the lungs at 4, 6, and 8 months in each of the treatment groups were of the same character but were more pronounced in the groups exposed to the mixtures. Reported effects included a thickening of the lung parenchyma with accumulation of lymphocytes, histiocytes, and fibroblasts, hyperplasia of the airways and blood vessel walls, and adenomas after several months.

Kitamura *et al.* (1980) exposed male Sprague-Dawley rats to a single dose of 23 mg/100 g b.w. of cemented tungsten carbide dust (presintered hard metal ground with a diamond wheel and administered intratracheally). Approximately 20% of the animals died within three days after exposure, and the lungs showed hemorrhagic edema with intense alveolar congestion. Surviving animals were killed at 6 months and 12 months. All animals killed at 6 months had pulmonary lesions of patchy fibrosis in the vicinity of deposited dust, but no definitive inflammatory reaction or interstitial pneumonitis (alveolitis) was found. At 12 months one-third of the animals continued to show similar effects in the lung while the remaining two-thirds had neither fibrosis nor dust deposits, showing regression of the lesions.

IARC (2006) reported results from a paper published in Japanese by Tozawa *et al.* (1981). The investigators administered a single intratracheal dose of presintered cemented carbides (WC:Co = 98:2 or WC:Co:TiC:TaC = 64:16:6:14) to male Sprague-Dawley rats [age not reported] and examined the effects after 6 and 12 months. Marked fibrotic foci were observed after 6 months but had decreased after 12 months. Cobalt was eliminated from the lung more rapidly than tungsten.

[1] Paper published in German; information reported is from the English abstract.

Lasfargues and coworkers studied the acute (Lasfargues *et al.* 1992) and delayed (Lasfargues *et al.* 1995) responses of female Sprague-Dawley rats to pure cobalt metal powder and cobalt–tungsten carbide powder (see Section 5.2.3 and Table 5-1 for acute cytotoxic effects). Intratracheal instillation of 1.0 mg cobalt/100 g b.w. resulted in 20% mortality within 24 hours but no marked changes in lung histology. The dose of 16.67 mg cobalt–tungsten carbide (equivalent to 1.0 mg cobalt)/100 g b.w. resulted in 60% mortality, and lung histology in these animals showed an acute and diffuse inflammatory reaction with generalized edematous alveolitis.

Adamis *et al.* (1997) compared the lung toxicity of samples of respirable cobalt–tungsten carbide obtained at three stages of the manufacturing process in a hard-metal producing plant: as finished powder for pressing (FP); from a heat-treated, presintered sample obtained at 800°C (PH), and from wet grinding of sintered hard metal obtained by heat treatment at 1,200°C (HM). Rats were killed for bronchoalveolar lavage (biochemical studies for cytotoxicity endpoints are summarized in Table 5-1) and histological studies at 1, 4, 7, and 30 days after treatment. Histological examination of the lungs showed fibrosing alveolitis that developed by 30 days with all three sample types.

Rengasamy *et al.* (1999) investigated the effects of an industrial hard-metal mixture on nitric oxide production, interactions between hard metals and lipopolysaccharide on nitric oxide pathways, and alterations in airway reactivity to methacholine in rat lungs. The tungsten:cobalt ratio was about 16:1 in the hard-metal mixture, which also contained smaller amounts of chromium and iron. Male Sprague-Dawley rats [age not reported] were dosed with a single intratracheal instillation of 2.5 to 5 mg/100 g b.w. Hard-metal exposure increased nitric oxide synthase (NOS) activity in rat lung at 24 hours, but there was no increase in inducible NOS or endothelial NOS mRNA abundance or inducible NOS, endothelial NOS, or brain NOS proteins. Intraperitoneal injection of lipopolysaccharide caused up-regulation of inducible NOS activity, mRNA, and protein at 8 hours but not at 24 hours. Basal airway obstruction and a marked hyporeactivity to inhaled methacholine occurred at 6 to 8 hours and intensified over 30 to 32 hours. Protein leakage into the alveolar space, edema, fibrin formation, and an increased number of inflammatory cells in the lungs and bronchoalveolar lavage were reported. The authors concluded that the hard-metal–induced increase in nitric oxide production by pulmonary inflammatory cells was associated with pulmonary airflow abnormalities in the rat lung.

### *5.2.3 Cytotoxicity studies*

Table 5-1 summarizes the study methods and results of *in vitro* and *in vivo* studies evaluating the cytotoxicity of cobalt–tungsten carbide. Two *in vivo* studies (intratracheal administration) showed greater toxic effects with cobalt–tungsten carbide than with cobalt powder alone in the lungs of female Sprague-Dawley rats (Huaux *et al.* 1995, Lasfargues *et al.* 1995). Cytotoxicity was measured by cell number, lactate dehydrogenase (LDH), total protein, *N*-acetyl-β-D-glucosaminidase (NAG), or albumin. Adamis *et al.* (1997) determined the cytotoxicity of respirable samples collected at different stages of the hard-metal manufacturing process. They tested finished powder for pressing (8% cobalt); heat-treated, presintered material (8% cobalt); and powder resulting from wet grinding of sintered hard metals (3% cobalt). Pathological changes were seen in

histological sections of the lungs with all three materials. The degree of lung toxicity varied among the three powders, with the presintered material being the most toxic.

Similar to the *in vivo* studies, *in vitro* studies using mouse peritoneal macrophages (Lison and Lauwerys 1990, 1992, 1994), rat alveolar macrophages (Lison and Lauwerys 1990, Roesems *et al.* 1997, Roesems *et al.* 2000), and rat type II pneumocytes (Roesems *et al.* 1997, Roesems *et al.* 2000) have also shown greater toxic effects with cobalt–tungsten carbide than with cobalt powder alone (study details are described in Table 5-1). No toxicity (as assessed by LDH release) was observed for either cobalt, tungsten, or cobalt–tungsten carbide in human type II pneumocytes (Roesems *et al.* 1997) or in another study of rat alveolar macrophages when toxicity was assessed by release of interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), fibronectin, or cystatin-c (Huaux *et al.* 1995).

[Although it often is assumed that the toxicity of metallic compounds is mediated by their solubilized ions, there is evidence that the toxic effects of hard-metal particles result, at least in part, from a surface-chemistry reaction occurring at the particulate level.] The *in vitro* toxicity of cobalt–tungsten carbide particles was greater than cobalt alone, but the synergistic effect was only observed when the cobalt and tungsten particles were in direct contact with cells (Lison and Lauwerys 1992, Roesems *et al.* 2000). Although cobalt solubilization was increased in the presence of tungsten carbide, the increased bioavailability of cobalt alone did not account for the greater toxicity of the mixture. The uptake of cobalt by mouse peritoneal macrophages was greater when the metal was in the form of hard-metal particles. However, the *in vitro* toxicity of hard-metal particles to mouse peritoneal macrophages was greater than cobalt alone even at equivalent intracellular cobalt concentrations (Lison and Lauwerys 1994). Several *in vitro* and *in vivo* experiments have demonstrated that a specific toxic reaction results from the interaction between cobalt metal and tungsten carbide particles and oxygen to produce reactive oxygen species. Thus, hard-metal dust behaves as a specific toxic entity (Lison and Lauwerys 1992). Furthermore, Lison and Lauwerys (1995) demonstrated a synergistic interaction between cobalt and other metallic carbide particles (i.e., titanium carbide, chromium carbide, and niobium carbide) in mouse peritoneal macrophages. This interaction was not observed with molybdenum, tantalum, or silicon carbides. The authors concluded that the interaction could not be attributed solely to an increased bioavailability of cobalt because cobalt uptake into macrophages was similar with the interactive and non-interactive carbides. However, the interaction seemed to depend on particle size since the interactive carbides contained at least 50% of fine particles (< 2 μm), and the powder with the smallest particle size (niobium carbide) produced the most intense response. Based on these data, the authors suggested that a physicochemical reaction taking place at the interface between certain carbides and cobalt particles might be responsible for the increased toxicity of the mixture.

Roesems *et al.* (2000) reported that the cytotoxic action of cobalt or cobalt–tungsten carbide could be reproduced partly or totally by treating the cells with leachate from these particles. The leachate was produced by placing the particles in an insert above the cells. Furthermore, cobalt chloride was also cytotoxic to rat lung cells. Based on these findings, the authors concluded that cobalt ions play a role in the toxicity of cobalt–tungsten carbide particles as well as cobalt particles. In contrast, Lison and Lauwerys (1992)

reported that cobalt chloride was not cytotoxic to mouse peritoneal macrophages and that solubilization of cobalt from the mixture was not a critical factor. Lison (2000) suggested that the difference in results was most likely due to the presence of protein (lactalbumin hydrolysate), which would bind the free cobalt ions, in the culture medium used in the studies by Lison and Lauwerys (1990, 1992). Lison (2000) believed that the cytotoxic action of cobalt ions in the absence of proteins was of limited biological relevance and that the toxicity of cobalt–tungsten carbide particles was independent of soluble components.

**Table 5-1. Cytotoxicity studies with cobalt–tungsten carbide powders**

| Test system (reference) | Endpoint(s) | Test agent | Results |
|---|---|---|---|
| ***In vivo* assays (lung toxicity after intratracheal instillation)** | | | |
| Female Sprague-Dawley rats<br>Huaux *et al.* 1995 | cellular (total and differential) counts, LDH, total protein, and albumin, in BALF | CoWC[a] (1 mg [0.06 mg Co]/100 g b.w.)<br>Co (0.06 mg/100 g b.w.)<br>WC (1 mg/100 g b.w.) | Cellular counts for BALF were not affected by Co or WC, but CoWC instillation caused significant ($P < 0.01$) increases in total cell number, macrophages, and neutrophils. LDH, total protein, and albumin were significantly increased after instillation with CoWC but not Co or WC alone. |
| Female Sprague-Dawley rats<br>Lasfargues *et al.* 1995 | cellular (total and differential) counts, LDH, NAG, total protein, and albumin, in BALF | CoWC[a] (1, 5, and 10 mg [0.06, 0.3, and 0.6 mg Co]/100 g b.w.)<br>Co (0.06, 0.3, and 0.6 mg/100 g b.w.)<br>WC (1, 5, and 10 mg/100 g b.w.) | Cell numbers (total cells, macrophages, neutrophils, and lymphocytes) were significantly increased at 1 and 28 days (except lymphocytes at 1 mg/100 g b.w.) after CoWC instillation at all doses, but Co increased numbers only at the highest dose and only at 1 day after treatment. LDH, NAG, total proteins, and albumin were significantly ($P < 0.01$) increased in BALF at 1 day after CoWC instillation while Co and WC caused significant ($P < 0.05$) increases only at the highest dose tested. |

| Test system (reference) | Endpoint(s) | Test agent | Results |
|---|---|---|---|
| Male Sprague-Dawley rats<br>Adamis *et al.* 1997 | LDH, acid phosphatase, protein, and phospholipid in cell-free BALF | respirable samples[b] collected at a hard-metal producing plant (administered at 1 or 3 mg/rat):<br>1) finished powder for pressing[c] (FP)<br>2) heat-treated, presintered sample obtained at 800°C[c] (PH)<br>3) wet grinding of sintered hard metal obtained by heat treatment at 1,200°C[d] (HM) | LDH activity increased after 4 days with administration of 3 mg of dust:<br>PH > HM > FP<br>The increase in acid phosphatase activity was mixed, with significant ($P < 0.05$ or $P < 0.01$) increases for each type of sample for at least one dose and time point up to day 7 but not at day 30.<br>Protein was significantly increased with the 1-mg dose of PH at 7 days, and both FP and PH were significant at 4 days with the 3-mg dose.<br>Significant increases in phospholipid were seen only with the 3-mg dose and only for HM (at 4 and 7 days) and PH (at 7 days). |
| ***In vitro* assays** | | | |
| Mouse peritoneal macrophages<br>Lison and Lauwerys 1992 | LDH release | CoWC[a] (100 μg/mL)<br>Co (6 μg/mL)<br>cobalt chloride (1, 10, 100, and 1,000 μM) | Only CoWC was toxic (increased LDH release), and only when in direct contact with the cells. |
| Mouse peritoneal macrophages<br>Lison and Lauwerys 1994 | LDH release | CoWC[a] (50 or 150 μg/mL)<br>Co (3, 9, or 20 μg/mL) | CoWC produced a greater toxic effect (increased LDH release) than Co alone even when the intracellular concentration of cobalt was the same. |
| Mouse peritoneal macrophages<br>Lison and Lauwerys 1990 | LDH release, morphology | CoWC[a]<br>Co<br>WC<br>12 to 590 μg dust/$10^6$ cells for each powder | CoWC was the most toxic entity tested (increased LDH release confirmed by electron microscopy), with no effect seen for WC alone and slight impairment of cell viability by cobalt metal powder. |

| Test system (reference) | Endpoint(s) | Test agent | Results |
|---|---|---|---|
| Rat alveolar macrophages<br>Huaux *et al.* 1995 | release of IL-1, TNF-α, fibronectin, and cystatin-c by lung phagocytes | CoWC[a] (50 μg/mL)<br>Co (3 μg/mL)<br>WC (50 μg/mL) | No significant effect on IL-1, TNF- α, fibronectin, or cystatin-c. |
| Rat alveolar macrophages<br>Roesems *et al.* 1997 | LDH release | CoWC[a]<br>Co<br>WC<br>0.118 to 1,180 μg/$10^5$ cells/200 μL/well for each powder | CoWC $TD_{50}$ (per $10^5$ cells ) = 5 μg<br>Co $TD_{50}$ (per $10^5$ cells) = 18 μg<br>WC $TD_{50}$ (per $10^5$ cells ) = 591 μg |
| Rat alveolar macrophages<br>Roesems *et al.* 2000 | MTT assay | CoWC[a] (83, 417, or 1,667 μg/700 μL/well)<br>Co (5, 25, or 100 μg/700 μL/well) | CoWC doses were selected to give equivalent dose of cobalt (2, 25, and 100 μg) and were approximately twice as toxic as cobalt ($P < 0.001$). |
| Rat alveolar macrophages<br>Lison and Lauwerys 1990 | LDH release, morphology | CoWC[a]<br>Co<br>WC<br>12 to 590 μg dust/$10^6$ cells for each powder | CoWC was the most toxic entity tested (increased LDH release confirmed by electron microscopy), with no effect seen for WC alone and slight impairment of cell viability by cobalt metal powder. |
| Rat type II pneumocytes<br>Roesems *et al.* 1997 | LDH release | CoWC[a]<br>Co<br>WC<br>0.118 to 1,180 μg/$10^5$ cells/200 μL/well for each powder | CoWC $TD_{50}$ (per $10^5$ cells ) = 101 μg<br>Co $TD_{50}$ (per $10^5$ cells) = 672 μg<br>WC $TD_{50}$ (per $10^5$ cells ) = 4,468 μg |
| Rat type II pneumocytes<br>Roesems *et al.* 2000 | MTT assay | CoWC[a] (83, 417, or 1,667 μg/700 μL/well)<br>Co (5, 25, or 100 μg/700 μL/well) | CoWC and Co showed similar toxicity |

| Test system (reference) | Endpoint(s) | Test agent | Results |
|---|---|---|---|
| Human type II pneumocytes<br>Roesems *et al.* 1997 | LDH release | CoWC[a]<br>Co<br>WC<br>0.118 to 1,180 μg/$10^5$ cells/200 μL/well for each powder | No toxicity observed for CoWC, Co, or WC. |

BALF = bronchoalveolar lavage fluid; Co = cobalt; CoWC = cobalt–tungsten carbide; IL-1 = interleukin-1; LDH = lactate dehydrogenase; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NAG = *N*-acetyl-β-D-glucosaminidase; $TD_{50}$ = toxic dose leading to 50% cell death; WC = tungsten carbide.
[a]Cobalt–tungsten carbide mixture prepared by a hard-metal producing factory (cobalt = 6.3%; tungsten = 84%; carbon = 5.4%).
[b]The authors reported that all particles were 0.1–5.0 μm in size, with average size around 1 μm.
[c]Cobalt = 8%; tungsten carbide = 90%; titanium carbide = 1%; silicium carbide = 0.1%.
[d]Cobalt = 3%; tungsten carbide = 40%; titanium carbide = 5%; silicium carbide = 25%; iron = 20%; sand (silica) = 5%.

### *5.2.4 Biochemical studies of reactive oxygen species formation*

Several lines of experimental evidence support a greater formation of reactive oxygen species (ROS) by the combination of a mixture of cobalt and tungsten carbide particles compared with cobalt metal particles alone. In a deoxyribose degradation assay to detect the capacity to generate hydroxyl radicals *in vitro,* the activity of cobalt metal particles was significantly increased (about threefold) by association with tungsten carbide particles (median diameter = 2 μm) (Lison and Lauwerys 1993). Through the use of electron spin resonance with a trapping reagent, it was shown that the production of hydroxyl radicals by cobalt metal particles in aqueous buffered suspension was minimal, but the production of free radicals was markedly increased in the presence of tungsten carbide particles (at a ratio of 6% cobalt to 94% tungsten carbide); both a laboratory-prepared mixture and powder from a hard-metal producing factory were tested (Lison *et al.* 1995). The ability of cobalt metal particles to produce ROS was observed in the absence of hydrogen peroxide and could not be fully reproduced with Co(II) ions, which Lison *et al.* concluded was an indication that soluble cobalt ions were the product of the reaction rather than its source, which would be typical of a Fenton-like mechanism. Kadiiska *et al.* (1989) reported that for Co(II) in the presence of hydrogen peroxide, superoxide formation predominated over production of hydroxyl radicals, and they also proposed that Co(II) did not react with hydrogen peroxide by a classical Fenton reaction.

However, Mao *et al.* (1996) and Leonard *et al.* (1998) demonstrated that the ability of Co(II) ions to generate ROS from hydrogen peroxide via a Fenton-like reaction could be increased by biological chelators such as anserine, glutathione, and glycylglycylhistidine and Mao *et al.* suggested that chelation in cellular systems could play a role in generation of ROS by Co(II) in those systems. Lison and coworkers (Lison *et al.* 2001) subsequently proposed that formation of ROS could result from either the interaction of cobalt metal and tungsten carbide or from the Co(II) ions generated from the Fenton-like reaction of the metal and carbide (see Section 5.5 and Figure 5-1).

Lison *et al.* (1995) also reported a significant ($P < 0.01$) increase in arachidonic acid peroxidation in the presence of the cobalt and tungsten carbide mixtures compared with either cobalt or tungsten carbide alone. When mouse peritoneal macrophages were incubated with cobalt–tungsten carbide particles, the concentration of the mixture that was toxic to 50% of the cells was increased threefold by the addition of BHT, an antioxidant. Based on these experimental results, the authors proposed that production of ROS is mediated by contact between the cobalt and tungsten carbide particles, which allows the rapid reduction of ambient oxygen; meanwhile, metallic cobalt is simultaneously solubilized as Co(II). In this solid-solid interaction, molecular oxygen is reduced at the surface of tungsten carbide particles through the flow of electrons from the cobalt atoms to the oxygen molecules. The cobalt is consequently oxidized to Co(II). Contrary to what happens in a Fenton-like reaction, Co(II) does not drive the production of ROS, but is the product of this reaction (Figure 5-1).

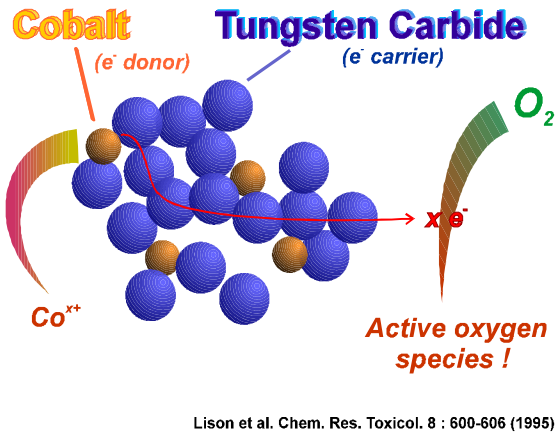


**Figure 5-1. Generation of ROS (identified as active oxygen species in the figure) by interaction between cobalt metal and tungsten carbide particles**

Further investigations of the surface interaction between cobalt metal and tungsten carbide particles prepared in the laboratory or obtained from a hard-metal production factory (Zanetti and Fubini 1997) indicate that the two associated solids may act as a distinct chemical entity. The authors concluded that the adsorption capacity and energy of adsorption for water vapor and the catalytic decomposition of hydrogen peroxide, which were higher than expected from the sum of the contributions by the two components, could only be explained by a chemical reaction or activation occurring at the interface between the components. Their joint presence thus provides a continual source of ROS. In this reaction, cobalt is more active than other metals (e.g., iron or nickel) (Fenoglio *et al.* 2000).

Keane *et al.* (2002) confirmed the generation of hydroxyl radicals by cobalt–tungsten carbide hard metals in aqueous suspension by examining the properties of detonation coating materials made of a mixture of cobalt and tungsten carbide (6.7% cobalt in the starting material and 5.4% cobalt in the dust remaining after detonation coating; see Section 2.3.4). The post-detonation material was a much stronger generator of hydroxyl radicals than the pre-detonation material.

Francia *et al.* (2007) investigated the electrochemical process responsible for free radical release in hard metals. They reported that the reaction can take place only when the tungsten carbide surface is covered with a thin layer of electrolyte, a situation similar to that encountered by cobalt–tungsten carbide particles in the distal parts of the lung. These authors assembled a voltaic cell corresponding to the overall spontaneous electrochemical process and demonstrated that cobalt in direct contact with tungsten carbide in an electrolyte-wet environment spontaneously and rapidly oxidizes in relation to the oxygen reduction catalyzed by tungsten carbide and that active oxygen species are produced.

[Overall, these experimental data indicate that the reaction of cobalt metal with ambient molecular oxygen is amplified when the particles are associated with tungsten carbide, i.e., in hard-metal particles.] Compared with cobalt metal alone, the rate of ROS formation and hence of cobalt solubilization is markedly increased in the hard-metal mixture. Lison *et al.* (2001) noted that both ROS and Co(II) ions can affect DNA integrity, and that both are likely involved in the mechanisms of genotoxicity of cobalt–tungsten carbide. ROS are involved directly or indirectly (e.g., via a lipoperoxidation process) in the clastogenic activity of cobalt–tungsten carbide hard metals (Lison *et al.* 2001). Genotoxic effects are discussed below in Section 5.3.

## 5.3 Genetic damage and related effects

Genotoxicity tests have been conducted with hard-metal particles *in vitro* and either isolated human blood lymphocytes or isolated mouse DNA. The potential genotoxic effect of hard-metal particles also has been examined *in vivo* in the lungs of rats after intratracheal administration. A single study examined a variety of genotoxicity biomarkers in workers from the hard-metal industry in Europe. The results obtained with hard-metal particles in these studies are summarized in Table 5-2 and reviewed below. The genotoxicity of soluble cobalt compounds is summarized in Section 5.4, and mechanisms of the genotoxicity of cobalt–tungsten carbide hard-metal particles are discussed in Section 5.5.

IARC reviewed the mutagenic effects of cobalt–tungsten carbide hard metals and cobalt compounds in October 2003 and concluded that when cobalt metal particles are mixed with tungsten carbide, a unique chemical entity is formed that produces higher amounts of ROS than cobalt alone, is more mutagenic *in vitro* in human cells than cobalt alone, and is mutagenic *in vivo* in rat lung cells (IARC 2006).

### *5.3.1 Prokaryotic and non-mammalian systems*

No studies on the potential genotoxicity of hard-metal particles in bacteria, yeast, or insects were identified.

### *5.3.2 Mammalian systems* in vitro

The clastogenic activity of a cobalt–tungsten carbide particle suspension was evaluated by measurement of DNA breaks and alkali-labile sites in the alkaline elution assay and by alkaline single-cell gel electrophoresis (the comet assay). Alkaline elution measures the rate of DNA elution through a filter membrane. An increase in the elution rate indicates DNA damage (single-strand breaks, or lesions converted to single-strand breaks under

alkaline conditions) (Anard *et al.* 1997). The comet assay uses electrophoresis at a high pH that results in migration of cellular DNA towards the anode. The appearance of a comet is formed when the DNA contains single-strand breaks, or lesions converted to single-strand breaks under alkaline conditions. The extent of DNA damage generally is determined by the percent comet tail intensity, tail length, or tail moment (i.e., the product of comet tail length and tail intensity). All of the cobalt–tungsten carbide used in these studies was laboratory prepared except the Anard *et al.* (1997) study, which used presintered cobalt–tungsten carbide powder. When tested in concurrent assays over a range of cobalt-equivalent concentrations, a mixture of cobalt and tungsten carbide (6% and 94% by weight, respectively) caused on average three times as many DNA breaks as cobalt metal particles alone, both in isolated mouse DNA (Anard *et al.* 1997) and in cultured human lymphocytes (Anard *et al.* 1997, De Boeck *et al.* 1998, Van Goethem *et al.* 1997). Dose and time dependency of DNA breakage and alkali-labile sites were characterized with the comet assay; significant DNA damage (increased percentage of tail DNA) was noted after a 15-minute incubation with cobalt–tungsten carbide particles at a concentration of 10 μg/mL (De Boeck *et al.* 1998). In the alkaline elution assay, the DNA strand-breaking activity of cobalt–tungsten carbide particles was inhibited in part by scavenging of ROS with formate (1 M) (Anard *et al.* 1997). However, the comet assay did not detect a significant increase in oxidatively damaged DNA as measured by formamidopyrimidine DNA glycosylase (Fpg)–sensitive sites, suggesting the formation of DNA adducts (e.g., related to lipid peroxidation products) rather than direct DNA oxidation by ROS (De Boeck *et al.* 1998). [Although no significant increase in Fpg-sensitive sites was observed, lesions detected by the Fpg enzyme represent only a fraction of the possible DNA lesions induced by oxidative stress (i.e., mainly oxidized purines like 8-hydroxydeoxyguanosine).] In concurrent assays, cobalt chloride (at a concentration of up to 1 mM) and cobalt metal particles alone produced significantly fewer DNA breaks or alkali-labile sites, and tungsten carbide alone was completely inactive (Anard *et al.* 1997, De Boeck *et al.* 1998), indicating that the cobalt–tungsten carbide mixture is a distinct genotoxicant.

A cobalt–tungsten carbide mixture also was more genotoxic than cobalt metal particles in the micronucleus assay in cytokinesis-blocked human lymphocytes *in vitro* (De Boeck *et al.* 2003a, Van Goethem *et al.* 1997). The lowest effective dose was the same for both materials tested, but overall the cobalt–tungsten carbide mixture had a stronger effect in both studies; Van Goethem *et al.* described it as significantly enhanced while De Boeck *et al.* reported that it was more pronounced but not statistically significant. Increased rates of micronucleus formation may reflect either clastogenic or aneugenic events. The mechanisms for the genotoxicity of cobalt–tungsten carbide particles may include clastogenic effects mediated by ROS produced at the surface of these particles and/or aneugenic effects mediated by Co(II) ions released from these particles, and possibly others (see Section 5.5 for further discussion of mechanisms).

More recently, this *in vitro* genotoxicity has been found with mixtures of cobalt metal with niobium carbide (NbC) and chromium carbide ($Cr_3C_2$); although these carbides alone did not induce micronucleus formation in human lymphocytes, cobalt alone and, to a greater extent, the carbide-cobalt mixtures induced a statistically significant concentration-dependent increase in micronucleated binucleated cells. Molybdenum

carbide ($Mo_2C$) particles, which have a much smaller specific surface area than niobium or chromium carbide particles, did not interact with cobalt particles in this test, consistent with the hypothesis that the genotoxic effect results, at least in part, from a surface-chemistry reaction (De Boeck *et al.* 2003a).

### *5.3.3 Rat* in vivo *systems*

A single intratracheal instillation of cobalt–tungsten carbide particles administered to male Wistar rats caused DNA strand breaks and alkali-labile sites (in the comet assay) and micronucleus formation in rat type II pneumocytes, in a dose- and time-dependent manner (De Boeck *et al.* 2003b). At a dose that caused mild pulmonary toxicity (16.6 mg/kg b.w.), cobalt–tungsten carbide particles significantly increased the percentage of tail DNA (at 12 hours) and the frequency of micronuclei (at 72 hours). The authors discussed two possible mechanisms to account for these genotoxic effects: the direct mutagenic activity of cobalt–tungsten carbide particles (as demonstrated *in vitro*) and the production of ROS by inflammatory cells recruited in the lung. In rat peripheral blood mononucleated cells, no increase in DNA damage or micronuclei was observed, indicating that circulating lymphocytes are poor reporter cells for monitoring the genotoxic effects of inhaled particles. The authors related this to the lack of systemic exposure to the hard-metal particles. However, the authors also suggested that peripheral blood mononucleated lymphocytes have potential as reporter cells for genotoxic damage in the lung based on a small, but not statistically significant, increase in micronucleated binucleated cells at 72 hours in positive-control (bleomycin-treated) animals in the same study. Bronchoalveolar lavage (BAL) cells of treated animals showed statistically significantly lower levels of DNA migration than controls. The authors stated that changes in the relative proportion of exposed versus non-exposed cells in the BAL fluid could have contributed to this observation.

**Table 5-2. Results of genotoxicity testing of hard-metal particles in mammalian systems *in vitro* and *in vivo***

| Test system | Particle[a,b] | End point | LED/HID (Co eq/mL) | Result | Reference |
|---|---|---|---|---|---|
| ***In vitro*** | | | | | |
| Mouse DNA (3T3 fibroblasts) | CoWC[c]<br>Co | DNA damage[d] | 0.5 µg<br>1 µg | +<br>+ | Anard *et al.* 1997 |
| Human isolated peripheral blood lymphocytes | CoWC<br>Co<br>WC | DNA damage[d] | 1.5 µg<br>3.0 µg<br>250 µg | +<br>+<br>– | Anard *et al.* 1997 |
| | CoWC<br>Co<br>WC | DNA damage[e] | 3 µg<br>4.5 µg<br>100 µg | +<br>+<br>– | |
| | CoWC<br>Co<br>WC | DNA damage[e] | 0.6 µg[f]<br>0.6 µg<br>10 µg | +<br>+<br>+ | Van Goethem *et al.* 1997 |
| | CoWC<br>Co | DNA damage[e] | 0.6 µg[f]<br>0.3 µg | +<br>+ | De Boeck *et al.* 1998 |
| | CoWC | Fpg-sensitive[e] sites | 6 µg | – | |

| Test system | Particle[a,b] | End point | LED/HID (Co eq/mL) | Result | Reference |
|---|---|---|---|---|---|
| | CoWC | DNA damage[e] | 0.6 μg | + | De Boeck *et al.* 2003a |
| | CoNbC | | 6 μg | + | |
| | $CoCr_3C_2$ | | 0.6 μg | + | |
| | $CoMo_2C$ | | 0.6 μg | + | |
| | Co | | 0.6 μg | + | |
| | WC | | 100 μg | – | |
| | CoWC | micronuclei in cytokinesis-blocked cells | 0.6 μg[f] | + | Van Goethem *et al.* 1997 |
| | Co | | 0.6 μg | + | |
| | WC | | 50 μg | + | |
| | CoWC | micronuclei in cytokinesis-blocked cells | 0.6 μg | + | De Boeck *et al.* 2003a |
| | CoNbC | | 3 μg | + | |
| | $CoCr_3C_2$ | | 3 μg | + | |
| | $CoMo_2C$ | | 6 μg | – | |
| | Co | | 3 μg | + | |
| | WC | | 50 μg | + | |
| ***In vivo* (Male Wistar rat- intratracheal instillation)** | | | | | |
| Type II pneumocytes | CoWC | DNA damage[e] | 16.6 mg/kg | + | De Boeck *et al.* 2003b |
| | | micronuclei | 16.6 mg/kg | + | |
| Peripheral-blood lymphocytes | CoWC | DNA damage[e] | 16.6 mg/kg | – | |
| | | micronuclei | 49.8 mg/kg | – | |
| BAL | CoWC | DNA damage[e] | 16.6 mg/kg | – | |

BAL = bronchoalveolar lavage cells; Co = cobalt; CoWC = cobalt–tungsten carbide; Co eq/mL = cobalt equivalent concentration for *in vitro* studies; $Cr_3C_2$ = chromium carbide; Fpg =formamidopyrimidine DNA glycosylase (measures oxidative damage); HID = highest ineffective dose; LED = lowest effective dose; $Mo_2C$ = molybdenum carbide; NbC = niobium carbide; WC = tungsten carbide.

[a]All cobalt–tungsten carbide used in these studies was laboratory prepared except Anard *et al.* (1997) which used presintered cobalt–tungsten carbide powder.

[b]Mediam diameter of particles: Co = 4 μm; WC = < 1 to 2 μm.

[c]Reconstituted pure mixture containing 6% cobalt and 94% tungsten carbide.

[d]Strand breaks or alkali-labile sites (alkaline elution).

[e]Strand breaks or alkali-labile sites (comet assay).

[f]Although LED for Co was lower or equal to CoWC, CoWC had a stronger effect than Co overall.

### *5.3.4 Human exposure* in vivo

The possible genotoxic effects of occupational exposure to hard-metal dust (cobalt–tungsten carbide) at the TLV-TWA limit for cobalt-containing dust (20 μg/m$^3$) was explored in a study using several end points (De Boeck *et al.* 2000). The study examined three groups of male workers: 35 workers (mean age = 38.5 ± 7.7 [SD] years, range = 27.7 to 55.3) exposed to cobalt dust from three refineries, 29 workers (mean age = 40.7 ± 12.4 years, range = 20.7 to 63.6) exposed to hard-metal particles from two hard-metal production plants, and 27 matched control subjects (mean age = 38.0 ± 8.8 years, range = 23.3 to 56.4) recruited from the administrative departments of the respective plants. Smoking habits were identical in the three groups. The geometric mean levels of urinary cobalt (expressed as micrograms of cobalt per gram of creatinine) were consistent with an average exposure at the TLV-TWA in cobalt workers (21.5 μg/g, range = 5.0 to 82.5) and hard-metal workers (19.9 μg/g, range = 4.0 to 129.9) and the absence of occupational exposure in controls (1.7 μg/g, range = 0.6 to 5.5).

The study design integrated complementary biomarkers of DNA damage: 8-hydroxydeoxyguanosine (8-OHdG) in urine, DNA single-strand breaks and Fpg-sensitive sites (used to detect oxidative damage to DNA; see Glossary for definition) in the comet assay, and the *in vitro* cytochalasin-B micronucleus test in blood lymphocytes. Micronuclei were scored both in binucleated and in mononucleated cells, to discriminate between micronuclei accumulated *in vivo* (mononucleates) and additional micronuclei expressed *in vitro* (binucleates). The results for biomarkers of genotoxicity did not differ significantly between controls and workers exposed to cobalt-containing dust or between workers exposed to cobalt-containing dust and hard-metal dust. The only significant difference observed was a higher frequency of micronuclei in cytokinesis-blocked lymphocytes in workers exposed to cobalt than in workers exposed to hard-metal dust. However, the frequencies did not differ significantly from those for the exposed workers' concurrent controls. Multiple regression analysis indicated that workers who smoked and were exposed to hard-metal dusts had significantly elevated 8-OHdG and micronucleus values. [The power to detect effects was limited by the small sample size and the use of blood lymphocytes, which are poorly sensitive reporter cells. Strengths of the study were that the workers were matched for smoking and drinking habits and came from more than one plant.]

Mateuca *et al.* (2005) followed up the *in vivo* genotoxicity study by De Boeck *et al.* (2000) of workers exposed to cobalt and hard-metal dusts and examined the influence of DNA repair enzyme polymorphisms on the genotoxicity endpoints. In the total population (exposed and controls), multiple regression analyses found that DNA strand breaks (as detected by the comet assay), binucleate micronucleus frequency, and 8-OHdG were all associated with the interaction between smoking and exposure. In addition, DNA strand breaks were influenced by the type of plant (higher among exposed workers from cobalt–tungsten carbide plants than workers from cobalt plants), and X-ray–cross complementing group 1 (XRCC1) polymorphisms and binucleate micronucleus frequency also were influenced by the type of plant (higher among workers from cobalt plants). Mononucleate micronuclei were associated with being a smoker and working in a cobalt–tungsten carbide plant and having variant genotypes for both XRCC3 and 8-oxo-guanine-DNA glycosylase/AP lyase (hOGG1). In the exposed population, XRCC3 and XRCC1 genotypes were related to single-strand breaks, and the presence of variants for both hOGG1 and XRCC3 was related to micronuclei frequency (mononucleates). In addition, the interaction between the type of plant and smoking status influenced micronuclei and 8-OHdG. While the authors felt that the strength of the study lay in genotyping combined with several genotoxicity parameters, they noted that the limited number of subjects was a relative weakness.

## 5.4 Carcinogenicity, toxicity, and genotoxicity of cobalt compounds, alloys, and powder or dust, and tungsten compounds and alloys

Because powders and hard metals of cobalt–tungsten carbide contain cobalt particles and release Co(II) ions, the information available on the potential genotoxicity and carcinogenicity of cobalt metal and soluble cobalt compounds, including cobalt sulfate, is relevant in evaluating the carcinogenicity of cobalt–tungsten carbide powders and hard metals. IARC (2006) concluded that cobalt metal without tungsten carbide was *possibly carcinogenic to humans* (Group 2B), and cobalt sulfate and other soluble cobalt (II) salts

were *possibly carcinogenic to humans* (Group 2B). Cobalt sulfate is listed in the *Report on Carcinogens, Eleventh Edition* as *reasonably anticipated to be a human carcinogen*, based on sufficient evidence in animals. An NTP background document reviewing the evidence concerning the carcinogenicity of cobalt sulfate is available (NTP 2002a).

### *5.4.1 Carcinogenicity of cobalt compounds in experimental animals*

The available studies on carcinogenicity of cobalt compounds in animals are summarized in Table 5-3. In a two-year inhalation study conducted by NTP (1998), cobalt sulfate heptahydrate induced lung tumors in mice and rats and adrenal tumors in female rats (Bucher *et al.* 1999). Other soluble cobalt compounds (cobalt chloride and naphthenate) produced local tumors at injection sites. No recent inhalation study of insoluble cobalt compounds was identified. Early studies with cobalt oxides found local tumors at injection sites and lung tumors after intratracheal instillation. Early studies with cobalt metal alone or in alloys found only local tumors at injection sites.

## Table 5-3. Summary of carcinogenicity studies of cobalt compounds in experimental animals

| Compound or alloy | Exposure route | Species (sex) | No./ group | Conc. or dose | Treatment schedule | Results |
|---|---|---|---|---|---|---|
| **Soluble cobalt compounds** | | | | | | |
| cobalt sulfate heptahydrate | inhalation | $B6C3F_1$ mice (M/F)<br>F344 rats (M/F) | 50 | 0.3, 1.0, or 3 mg/m$^3$ | 5 d/wk, 6 h/d for 105 wk | lung tumors (all), adrenal tumors (female rats) |
| cobalt chloride | subcutaneous (s.c.) injection | Wistar rats (M) | 20 | 40 mg/kg | 10 injections (5 daily injections repeated once after 9-d interval) | injection-site and distant tumors |
| cobalt naphthenate | intramuscular (i.m.) injection | mice (NR) | 30 | 0.2 mg | NR | injection-site tumors |
| | i.m., intravenous (i.v.), intrapleural, or intrahepatic | rabbits (M) | 12 | NR | NR | injection-site tumors |
| cobalt(III) acetate | intraperitoneal (i.p.) injection | Strain A mice (M/F) | 10 | 95, 237, or 475 mg/kg (total) | 3 d/wk for 8 wk | lung tumors in exposed groups and controls (NS) |
| **Insoluble cobalt compounds** | | | | | | |
| cobalt(II) oxide | inhalation | Syrian hamsters (M) | 51 | 10 mg/m$^3$ | 5 d/wk, 7 h/d for life | NTR |
| | intratracheal instillation | Sprague-Dawley rats (M/F) | 50 | 2 or 10 mg/kg | every 2 wk (27 doses), then every 4 wk (12 doses) for 2 yr | lung tumors |
| | s.c. | Sprague-Dawley rats (M) | 10 | 2 mg/kg<br>10 mg/kg | 5 d/wk for 2 yr<br>1 d/wk for 2 yr | injection-site tumors |
| | i.p. | Sprague-Dawley rats (M/F) | 10 | 200 mg/kg | 3 injections at 2-mo intervals | injection-site tumors |
| | i.m. | Swiss mice (F) | 25–50 | 10 mg | single injection | NTR |
| | | Wistar rats (M/F) | 10 | 30 mg | single injection | injection-site tumors |
| | | Wistar rats (M/F) | 5–19 | 20 mg | single injection or 2 simultaneous injections (each thigh) | injection-site tumors |

| Compound or alloy | Exposure route | Species (sex) | No./ group | Conc. or dose | Treatment schedule | Results |
|---|---|---|---|---|---|---|
| cobalt(II) oxide & benzo[*a*]pyrene (B[*a*]P) | intratracheal | Sprague-Dawley rats (F) | 20 | (10 mg/kg × 7) + (20 mg/kg × 20) + (20 mg/kg × 10 B[*a*]P) | weekly (7 doses), then every 2 wk (20 doses) alternating with 10 doses of B[*a*]P | more lung tumors than B[*a*]P alone |
| cobalt(II,III) oxide & *N*-nitrosodiethylamine (NDEA) | intratracheal | hamsters (M/F) | 25 | 4 mg | weekly for 30 wk, following 12 weekly s.c. injections of 0.5 mg NDEA | no promoting effect |
| cobalt(II) sulfide | intrarenal | Sprague-Dawley rats (F) | 18 or 20 | 5 mg | single injection | NTR |
| | i.m. | Wistar rats (M/F) | 30 | 20 mg | simultaneous injections in each thigh | injection-site tumors |
| **Cobalt alloys** | | | | | | |
| Co-Al-Cr spinel | intratracheal | Sprague-Dawley rats (M/F) | 50 | 10 mg | every 2 wk (27 doses), then every 4 wk (12 doses) for 2 yr | lung tumors |
| | i.p. | Sprague-Dawley rats (M/F) | 10 | 600 mg/kg (total dose) | 3 injections at 2-mo intervals, observed for life | 2 injection-site tumors vs. 1 in controls |
| Co-Cr-Mo | s.c. | Wistar rats (M/F) | 5 | 4 pellets | pellets ~2-mm diameter, observed up to 27 mo | NTR |
| | i.m. | Wistar and Hooded rats (F) | 51–61 | 28 mg | single implant, observed for life | NTR |
| | i.m. | Dunkin-Hartley guinea-pigs (F) | 46 | 28 mg | single implant, observed for life | NTR |
| | intra-osseous, s.c. | rats (M/F) | 52 | NR | single implant (metal cylinder fixed on the femur) or single injection of microsphere suspension | implant & injection-site tumors |
| Co-Cr | intra-articular | rats (NR) | NR | NR | single injection into the knee, observed up to 1 yr | NTR |

| Compound or alloy | Exposure route | Species (sex) | No./ group | Conc. or dose | Treatment schedule | Results |
|---|---|---|---|---|---|---|
| Co-Cr-Mo wear particles | i.m. | hooded rats (F) | 80 (total) | 28 mg | single injection, observed up to 29 mo | injection-site tumors |
| | intra-articular | F344 rats (M) | 8–12 | 20 mg | single injection, observed for 24 mo | NTR |
| wrought Vitallium[a]<br>cast Vitallium[b]<br>$MP_{35}N$ alloy[c] | i.m. | Sprague-Dawley rats (M/F) | 15 | 1.6- × 8-mm rods | single implant, observed up to 2 yr | NTR |
| Co-Cr-Ni<br>Co-Mo<br>Co-W<br>Co-Zr<br>Co-W-Zr | intra-osseous | Sprague-Dawley rats (M/F) | 8–17 | 1.6- × 4-mm rods, powders, or porous compacted wire | single implant (femur), observed up to 30 mo | injection-site tumors in some groups, none in others |
| **Cobalt powder or dust** | | | | | | |
| Cobalt powder/dust | inhalation | rats (NR) | NR | 200 mg/$m^3$ | 12 h every other day for 4 mo, observed ≥ 4 mo | NTR |
| | | albino rabbits (M) | 12 | 1.5 mg/$m^3$ | 6 h/d every 3rd wk for 24 wk, observed ≥ 6 mo | NTR |
| | | miniature swine (NR) | 5 | 0.1 or 1 mg/$m^3$ | 6 h/d, 5 d/wk, for 3 mo, observed ≥ 3 mo | NTR |
| | intratracheal | rats (NR) | NR | 3–10 mg | 8 mo, observed ≥ 8 mo | NTR |
| | | guinea-pigs (NR) | 6 | 25 mg | single injection, observed 360 d | NTR |
| | | guinea-pigs (NR) | 6 | 2.5 mg | injections one wk apart, observed 360 d | NTR |
| | | guinea-pigs (NR) | NR | 5 mg | 2 injections one wk apart, observed 1 yr | NTR |
| | | guinea-pigs (NR) | NR | 25 mg | single injection, observed ≥ 8 mo | NTR |
| | | guinea-pigs (NR) | 6 | 50 mg | single injection, observed 1 yr | NTR |
| | | guinea-pigs (NR) | NR | 50 mg | single injection, observed ≥ 1 yr | NTR |

| Compound or alloy | Exposure route | Species (sex) | No./ group | Conc. or dose | Treatment schedule | Results |
|---|---|---|---|---|---|---|
| | i.m. | hooded rats (M/F) | 10 | 28 mg | single injection, observed 7.5 mo | injection-site tumors both sexes |
| | | hooded rats (M/F) | 10–20 | 28 mg | single injection, observed 5–12 mo, then females received 2nd injection | injection-site tumors both sexes |
| | | hooded rats (M) | 30 | 28 mg | single injection, observed ≥ 20 wk | tumor nodule in 1 rat |
| | intrathoracic | hooded rats (F) | 10 | 28 mg | single injection, observed up to 28 mo | injection-site tumors |
| | intrarenal | Sprague-Dawley rats (F) | 18 | 5 mg | single injection, observed up to 1 yr | NTR |

Sources: Bouchard *et al.* 1996, Howie and Vernon-Roberts 1988, IARC 1991, Lewis *et al.* 1995, NTP 1998, 2002b, see also reviews by Lewis and Sunderman 1996, Sunderman 1989.
NR = not reported; NTR = no tumors reported.
[a]19%–20% Cr, 14%–16% W, 9%–11% Ni, < 3% Fe, < 2% Mn, < 1% Si, < 0.15% C, balance Co [~47%–52%].
[b]27%–30% Cr, 5%–7% Mo, < 2.5% Ni, < 0.75% Fe, < 1% Mn, < 1% Si, < 0.3% C, balance Co [~57.5%–62.5%].
[c]19%–21% Cr, 9.5%–10.5% Mo, 33%–37% Ni, < 1% Fe, <0.15% Mn, < 0.15% Si, < 0.025% C, 0.65%–1% Ti, balance Co [~29%–36%].

### *5.4.2 Toxicity and genotoxicity of cobalt compounds*

The health effects reported for exposure to cobalt (as part of various individual cobalt compounds) include respiratory toxicity, skin allergy, goiter and reduced thyroid activity, cardiotoxicity, polycythemia, and reproductive effects (for more information, see review by Barceloux 1999). In occupational settings, the respiratory effects are the main health effects of concern. These effects consist of upper airway irritation, bronchial asthma, fibrosing alveolitis, and possibly lung cancer. Fibrosing alveolitis occurs almost exclusively in a small fraction of workers employed in hard-metal producing facilities (Lison *et al.* 1996) (see Section 5.2.1).

Like other metallic forms, Co(II) compounds are relatively inactive in prokaryotic systems (Rossman 1981, Swierenga *et al.* 1987). In mammalian cells, the results of the assays with soluble Co(II) salts clearly demonstrated their mutagenic potential (reviewed by De Boeck *et al.* 2003c). Two molecular mechanisms seem to apply: (1) a direct effect of Co(II) ions to damage DNA through a Fenton-like mechanism (e.g., Mao *et al.* 1996) and (2) an indirect effect through inhibition of the repair of DNA damage caused by endogenous events or other agents (e.g., Kasten *et al.* 1997). The ability of Co(II) ions to compete with other species in the zinc-finger domains of proteins involved in cell-cycle control and/or DNA repair may help to explain the latter effect of these cations (Hartwig *et al.* 2002).

Hartwig (2000) and Hartwig *et al* (2002) reported that a number of carcinogenic metals, including cobalt, interfere with DNA repair processes at low, noncytotoxic concentrations. Repair of DNA damage is vital for maintaining genomic integrity; thus, inactivation of DNA repair may be an important mechanism of metal-related carcinogenicity. Cobalt compounds are comutagenic in bacteria and mammalian cells, affect both the incision and the polymerization of repair patches, and disturb cell-cycle progression and control in response to ultraviolet C radiation. Interaction with zinc-finger proteins, which are involved in DNA binding and protein-protein interactions, were identified as potential molecular targets for metal ions. Cobalt inhibited mammalian xeroderma pigmentosum group A protein (XPA) and the poly(adenosine diphosphate-ribose)polymerase (PARP), but not the bacterial formamidopyrimidine-DNA glycosylase (Fpg). XPA is essential for DNA damage recognition during nucleotide excision repair, and PARP directs repair enzymes to the sites of damage and plays a role in apoptosis. In addition, the p53 protein is another zinc-dependent transcription factor involved in cell-cycle control and apoptosis. Cobalt also inhibits its DNA-binding activity.

Hartwig (2000) also reported that cobalt compounds damage DNA in the presence of reactive oxygen species. Cobalt ions and other carcinogenic metals are known to perform redox reactions in biological systems (Beyersmann and Hartwig 2008). These reactions result in reactive oxygen and nitrogen species *in vivo* and *in vitro* in mammalian cells. Fenton and Haber-Weiss–type reactions are likely responsible for the formation of hydroxyl radicals that can cause oxidative damage to lipids, proteins, and DNA. [Therefore, oxidative stress is not the sole cause for metal carcinogenesis but is likely a contributing factor.] Nackerdien *et al.* (1991) investigated the ability of cobalt(II) ions in the presence of hydrogen peroxide to cause chemical changes in DNA bases in chromatin extracted from human K562 cells. The typical hydroxyl radical-induced products of DNA bases were identified. Hydroxyl-radical scavengers resulted in partial inhibition of product

formation, while chelation of cobalt(II) ions with EDTA resulted in an almost complete inhibition of product formation. In an *in vivo* study, Kasprzak *et al.* (1994) reported oxidative DNA base damage in renal, hepatic, and pulmonary chromatin of rats after i.p. injection of 50 or 100 μmol cobalt(II) acetate. The bases were typical products of hydroxyl radical attack on DNA and showed increases of 30% to more than 200% over control levels.

These molecular mechanisms apply to soluble cobalt compounds, such as cobalt chloride or sulfate, and also to cobalt metal and hard-metal particles, which are readily solubilized in biological media. *In vivo*, however, the bioavailability of Co(II) is relatively limited, because these cations precipitate in the presence of physiological concentrations of phosphates ($K_{sp} = 2.05 \times 10^{-35}$ at 25°C) (CRC 1999) and bind to proteins such as albumin.

The genotoxicity data available for cobalt compounds are summarized in Table 5-4.

**Table 5-4. Results of genotoxicity testing of cobalt compounds and cobalt metal (without exogenous metabolic activation)**

| Cobalt compound | Test system | Effect | Result | References |
|---|---|---|---|---|
| **Prokaryotic** | | | | |
| cobalt chloride | *Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537, TA1538, TA2637 (Ames assay) | reverse mutation | –<br>–<br>–<br>–<br>±[a] | Tso and Fung 1981<br>Mochizuki and Kada 1982<br>Arlauskas *et al.* 1985<br>Ogawa *et al.* 1986<br>Wong 1988 |
| | *Bacillus subtilis* (rec assay) | growth inhibition | –<br>+ | Nishioka 1975<br>Kanematsu *et al.* 1980 |
| | *Escherichia coli* (reversion assay) | reverse mutation | –<br>– | Kada and Kanematsu 1978<br>Arlauskas *et al.* 1985 |
| | *E. coli* WP2s (λ) | λ prophage induction | – | Rossman *et al.* 1984 |
| cobalt sulfate | *S. typhimurium* TA97, TA98, TA100, TA1535 (Ames assay) | reverse mutation | (+) | Zeiger *et al.* 1992 |
| cobalt (III) complexes | *S. typhimurium* TA92, TA98, TA100 (Ames assay) | reverse mutation | +[b] | Schultz *et al.* 1982 |
| | *S. typhimurium* TA1535, TA1537, TA1538 (Ames assay) | reverse mutation | – | |
| | *E. coli* (repair assay) | DNA damage | +[c] | |
| cobalt sulfate | *B. subtilis* (rec assay) | growth inhibition | (+) | Kanematsu *et al.* 1980 |
| cobalt hydroxide | *B. subtilis* (rec assay) | growth inhibition | (+) | |
| cobalt carbonate | *B. subtilis* (rec assay) | growth inhibition | (+) | |
| cobalt carbonate + cobalt hydroxide | *B. subtilis* (rec assay) | growth inhibition | (+) | |
| **Yeast** | | | | |
| cobalt chloride | *Saccharomyces cerevisiae* (plate assay) | gene conversion (*trp* locus) | +<br>(+)<br>+ | Fukunaga *et al.* 1982<br>Singh 1983<br>Kharab and Singh 1985 |
| | *S. cerevisiae* (plate assay) | reverse mutation (*ilv* locus) | –<br>–<br>(+) | Fukunaga *et al.* 1982<br>Singh 1983<br>Kharab and Singh 1985 |
| | *S. cerevisiae* (plate assay) | *petite* mutation ($p^-$) | +<br>+<br>+<br>+<br>+ | Lindegren *et al.* 1958<br>Prazmo *et al.* 1975<br>Putrament *et al.* 1977<br>Egilsson *et al.* 1979<br>Kharab and Singh 1987 |

| Cobalt compound | Test system | Effect | Result | References |
|---|---|---|---|---|
| **Mammalian *in vitro*** | | | | |
| cobalt chloride | Chinese hamster ovary (CHO) cells (alkaline sucrose sedimentation) | DNA strand breaks | + | Hamilton-Koch *et al.* 1986 |
| | Chinese hamster ovary V79 cells | HPRT mutations | (+)<br>+ | Miyaki *et al.* 1979<br>Hartwig *et al.* 1990 |
| | mouse macrophage P388D1 cells | sister chromatid exchange (SCE) | + | Andersen 1983 |
| | human lymphocytes | chromosomal aberrations | – | Olivero *et al.* 1995 |
| | human lymphocytes | micronuclei | + | |
| | human lymphocytes (comet assay) | DNA damage | + | De Boeck *et al.* 1998 |
| | human fibroblasts (alkaline sucrose sedimentation and nick translation) | DNA strand breaks | + | Hamilton-Koch *et al.* 1986 |
| | human lymphocytes (fluorescence analysis) | DNA strand breaks | + | McLean *et al.* 1982 |
| | human lymphocytes | SCE | + | Andersen 1983 |
| | human lymphocytes (karyotype analysis) | aneuploidy | + | Resende de Souza-Nazareth 1976 (as cited in De Boeck *et al.* 2003c) |
| | HeLa cells | inhibition of DNA synthesis | + | Painter and Howard 1982 |
| | HeLa cells (nucleoid sedimentation) | DNA strand breaks | + | Hartwig *et al.* 1990 |
| | human leukocytes (comet assay) | DNA damage | – | Colognato *et al.* 2008 |
| | human whole blood | micronuclei | + | |
| cobalt sulfate | Syrian hamster embryo (SHE) cells | cell transformation | + | Kerckaert *et al.* 1996a,b |
| | mouse fibroblast NCTC 929 cells | induction of tumor suppressor protein p53 cells | + | Duerksen-Hughes *et al.* 1999 |
| | human lymphocytes | chromosomal aberrations | – | Olivero *et al.* 1995 |
| | human lymphocytes | micronuclei | – | |
| | human c-Ha-*ras*-1-protooncogene DNA fragments (gel electrophoresis) | DNA damage (with sodium sulfite) | + | Kawanishi *et al.* 1989 |
| | chromatin from human K562 cells (GC/MS-SIM detection of free-radical induced products) | chemical changes in DNA bases (with hydrogen peroxide) | + | Nackerdien *et al.* 1991 |
| cobalt nitrate | human lymphocytes | chromosomal aberrations | – | Olivero *et al.* 1995 |
| | human lymphocytes | micronuclei | – | |
| | human leucocytes | chromosomal aberrations | – | Paton and Allison 1972 |
| | human fibroblasts | chromosomal aberrations | – | |
| cobalt sulfide | CHO cells (alkaline sucrose gradient, molecular weight analysis) | DNA strand breaks | + | Robison *et al.* 1982 |
| | SHE cells | cell transformation | + | Costa *et al.* 1982 |

| Cobalt compound | Test system | Effect | Result | References |
|---|---|---|---|---|
| cobalt metal | human lymphocytes (comet assay and alkaline elution) | DNA strand breaks | + | Anard *et al.* 1997 |
| | human lymphocytes (comet assay) | DNA damage | + | De Boeck *et al.* 1998 |
| | human osteosarcoma cells (alkaline elution) | DNA breaks | – | Miller *et al.* 2001 |
| | human lymphocytes (comet assay) | DNA damage | +<br>– | Van Goethem *et al.* 1997<br>De Boeck *et al.* 2003a |
| | human lymphocytes (cytochalsin B) | micronuclei | +<br>+<br>+ | Van Goethem *et al.* 1997<br>Miller *et al.* 2001<br>De Boeck *et al.* 2003a |
| cobalt molybdate | SHE cells (simian adenovirus SA7) | cell transformation | + | Casto *et al.* 1979 |
| cobalt nanoparticles | human leukocytes (comet assay) | DNA damage | + | Colognato *et al.* 2008 |
| | human whole blood | micronuclei | + | |
| **Mammalian *in vivo*** | | | | |
| cobalt chloride | Syrian hamster bone marrow and testes [test system not reported] | aneuploidy | + | Farah *et al.* 1983 (as cited in De Boeck *et al.* 2003c) |
| | mouse bone marrow | chromosomal aberrations | + | Palit *et al.* 1991 (as cited in De Boeck *et al.* 2003c) |
| cobalt acetate | rat kidney, liver, and lung (GC/MS) | DNA base damage | + | Kasprzak *et al.* 1994 |

– = negative, + = positive, (+) = weakly positive, ± = positive and negative results reported.

[a] Negative for TA102 and TA1535; positive (without metabolic activation but not with metabolic activation for TA98 and TA1537.

[b] Positive in 4 of 15 complexes tested.

[c] Positive or weakly positive in 8 of 15 complexes tested.

### 5.4.3 Toxicity of tungsten carbide and tungsten compounds

No information is available on the health effects of exposure to tungsten carbide. However, several studies (Sahle 1992, Sahle *et al.* 1996, Sahle *et al.* 1994) suggest that a potential toxic effect of tungsten oxide fibers (whiskers) on the lungs of exposed workers should be investigated, based on reports that tungsten oxide fibers are cytotoxic to human lung cells and on the hypothesis that oxygen free radicals are involved in the toxicity of mineral fibers.

The experimental toxicity of tungsten compounds was reviewed by Wennig and Kirsch (1988). Soluble compounds are rapidly absorbed following ingestion and excreted in the urine (40%) and feces (58%) within 24 hours in rats. Lombaert *et al.* (2004) reported minimal solubilization (about 2%) of tungsten from cobalt–tungsten carbide particles in culture medium containing 15% serum after 24 hours. The tungsten carbide particles were phagocytosed by monocytes (see Section 5.5). Sodium tungstate ($Na_2WO_4$), a soluble tungsten salt, was reported to be moderately toxic by ingestion (Wennig and Kirsch 1988). Acute effects of this compound included central nervous system disturbances, diarrhea, respiratory failure, and death. Chronic exposure in rats resulted in reduced body weight, reduction of albumin, SH groups, γ-globulin, and uric acid in blood, and affected sperm motility. Tumor induction, body weight, and survival were not affected in rats exposed to 5 mg/L $Na_2WO_4$ in drinking water for life. Hard-metal workers had no allergic reactions to $Na_2WO_4$ in patch tests. Another compound, tungsten hexafluoride ($WF_6$) reacts with water to release hydrogen fluoride and can cause respiratory tract irritation, laryngitis, bronchitis, cyanosis, and pulmonary edema. *In utero* exposure to tungsten compounds resulted in embryo lethality and disturbance of skeletal ossification in rats and increased frequency of resorptions in mice.

### 5.4.4 Carcinogenicity and genotoxicity of tungsten compounds and alloys

Wei *et al.* (1985) investigated the effects of molybdenum and tungsten on mammary carcinogenesis in Sprague-Dawley rats. Female rats (35 days old) were randomly divided into four groups. Groups 1 through 3 were fed a nutritionally adequate diet and demineralized water, while group 4 was given the same diet with 150-ppm tungsten added to the drinking water. At 50 days of age, rats in groups 2 through 4 (22 to 24 animals) were injected via the tail vein with 5 mg/100 g b.w. of *N*-nitroso-*N*-methylurea (NMU). Group 1 (10 animals) received injections of the saline vehicle and served as the untreated controls. One week after treatment with NMU, 10-ppm molybdenum was added to the drinking water of group 3. Animals were sacrificed 125 days or 198 days after NMU treatment. Body-weight gains were slightly lower in the NMU-treatment groups compared with the controls. Mammary tumors appeared earlier in the tungsten treatment group (group 4). There was a significant increase in the incidence of mammary carcinomas in group 4 (79.2%) compared with group 2 (50%) after 125 days, but at 198 days, the incidences were similar (90.5% in group 2 and 95.7% in group 4). The tumor incidence in group 3 was 45.5% at 125 days and 50% at 198 days. No tumors occurred in the untreated controls. [The potential promoting effect of tungsten on nitrosamine-initiated cancer could be important because cutting fluids used to lubricate hard metal cutting tools may contain nitrosamines.]

Kalinich *et al*. (2005) reported that male F344 rats implanted intramuscularly (hind legs) with tungsten alloy pellets (91.1% tungsten, 6.0% nickel, and 2.9% cobalt) developed high-grade pleomorphic rhabdomyosarcomas at the site of implantation. These tumors, which metastasized rapidly to the lung, developed in all rats (N = 46) implanted with 20 tungsten alloy pellets (high dose) and in all rats (N = 46) implanted with 4 tungsten alloy pellets plus 16 titanium pellets (low dose) divided evenly between the hind legs. Rats (N = 36) implanted with 20 nickel pellets as a positive control also developed tumors, but the tumors developed at a slower rate than those in the tungsten-alloy–implanted rats. Rats (N = 46) in a negative control group implanted with 20 tantalum pellets did not develop tumors.

Miller *et al.* (2001) had previously demonstrated that a mixture of tungsten, nickel, and cobalt particles in similar proportions (92% tungsten, 5% nickel, and 3% cobalt) to those of the tungsten alloy implants resulted in approximately nine-fold increases in transformation frequency, approximately three-fold increases ($P < 0.01$) in induction of micronuclei, and 8.5- to 9-fold ($P < 0.001$) increases in the number of DNA single-strand breaks in a human osteosarcoma (HOS) cell model. Interestingly, the authors also demonstrated that a mixture of tungsten (92%), nickel (5%), and iron particles (3%) tested in the same system produced very similar results for the cell transformation and genotoxicity endpoints. Further tests with the tungsten, nickel, and cobalt mixture (designed to simulate alloys used in military applications) were conducted using HOS (Miller *et al.* 2002) and human liver carcinoma (HepG2) cells (Miller *et al.* 2004). Cultured HOS or HepG2 cells were incubated with the metal powder for 24 hours to assess morphological cell transformation. Cytogenetic analyses also were conducted to determine micronuclei, SCE, and DNA single-strand breaks (Miller *et al.* 2002). Miller *et al.* (2004) investigated the ability of the tungsten, nickel, and cobalt mixture and the pure metals to induce stress genes in 13 different recombinant cell lines in HepG2 cells. These studies indicated that the tungsten mixture could transform human cells to the tumorigenic phenotype through induction of DNA and chromosome damage. The mixture showed dose-related induction of GSTYA, hMTIIA, p53RE, FOS, NFκBRE, HSP70, and CRE promoters. Each of the individual metals showed a similar pattern of gene induction, but at a significantly lower level than the mixture.

## 5.5 Mechanistic studies and considerations

There is limited information about the mechanisms by which cobalt–tungsten carbide may cause toxicity and cancer. The proposed mechanisms primarily relate to effects (mainly genotoxic) mediated by simultaneous exposure to cobalt metal and tungsten carbide particles, and effects (both genotoxic and non-genotoxic) mediated by solubilized cobalt ions. Carcinogenicity and genotoxicity studies on cobalt compounds and tungsten compounds or alloys were discussed in Section 5.4.

This section discusses (1) solubilization and phagocytosis of cobalt and tungsten from cobalt–tungsten carbide hard metals, (2) related effects from cobalt–tungsten carbide and solubilized cobalt, (3) gene expression and apoptosis studies of cobalt–tungsten carbide, and (4) other effects, such as hypoxia-related effects, due to cobalt ions.

### *5.5.1 Solubilization studies*

Several studies have shown that cobalt ions can be solubilized from cobalt–tungsten hard metal particles in biological media. Stopford *et al.* (2003) reported similar cobalt solubilities (2.6% to 26.7%) for both pre- and post-sintered cobalt–tungsten carbide particles in artificial human tissue fluids and serum. Lombaert *et al.* (2004) exposed peripheral blood mononucleated cells, lymphocytes, and co-sedimenting monocytes to cobalt–tungsten carbide and found that about 77.5% of the cobalt particles were solubilized within 15 minutes, and were completely solubilized after 24 hours. Tungsten carbide particles did not dissolve but were phagocytosed by monocytes. [Thus, particulate metals such as insoluble cobalt compounds and tungsten carbide could be phagocytosed by non-macrophage cells in the respiratory tract. This could possibly lead to intracellular metal accumulation at very high levels. Even a small amount of dissolution of the metal ions could generate high soluble metal ion levels in the target cells.].

[The importance of phagocytosis and metal dissolution has been observed for other metals. Costa *et al.* (1982) reported that crystalline nickel, cobalt, and other heavy metal sulfides were actively phagocytosed by Chinese hamster ovary cells and induced morphological transformation in Syrian hamster embryo cells in a concentration-dependent fashion. However, the respective amorphous metal sulfide particles were not actively phagocytosed, and they induced considerably less morphological transformation. Furthermore, phagocytized inert particles (latex beads) did not induce transformation or DNA damage. [These data suggest that genotoxic dissolution products of the heavy metals are responsible for the observed DNA damage and cell transformation.]

### *5.5.2 Genetic and related effects of cobalt tungsten carbide and solubilized cobalt*

The genotoxic effects of cobalt–tungsten carbide particles may be due to ionic cobalt forms dissolved in biological media and/or to ROS produced at the solid-liquid interface (See Figure 5-2).

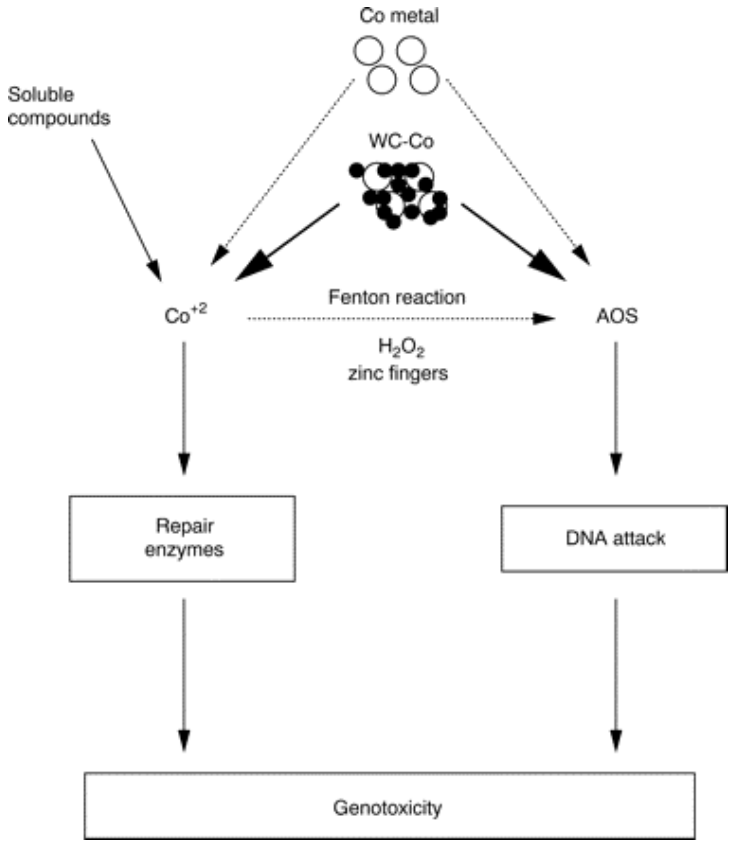


**Figure 5-2. Mechanisms of genotoxicity of cobalt–tungsten carbide (CoWC) hard metal and cobalt**

The proposed involvement of $Co^{2+}$ (which may inhibit DNA repair enzymes) and AOS (activated oxygen species, which are equivalent to ROS or reactive oxygen species and may attack DNA directly) generated from cobalt–tungsten carbide hard metal, cobalt metal, or soluble cobalt ions is illustrated. The arrow between $Co^{2+}$ and AOS denotes both the formation of AOS as a result of the participation of $Co^{2+}$ in a Fenton reaction and the formation of both AOS and $Co^{2+}$ from the Fenton-like reaction involving cobalt and tungsten carbide.

Source: Lison *et al.* 2001

### *Surface chemistry reaction of cobalt–tungsten carbide*

Lombaert *et al.* (2008) concluded that the available data indicate that simultaneous exposure to cobalt metal and tungsten carbide particles is required to exert genotoxic effects, which might be an important factor in the potential carcinogenicity of hard metals. Lison *et al.* (2001) reviewed the evidence comparing the genotoxicity of cobalt compounds and cobalt–tungsten carbide hard metals from their studies and those of other investigators. Hard-metal (cobalt–tungsten carbide) particles caused significantly more (approximately threefold) DNA breaks than were detected with cobalt metal particles alone for both isolated human DNA and cultured human lymphocytes by the alkaline gel electrophoresis (comet) assay. The genotoxic activity of cobalt–tungsten carbide also was greater than that of cobalt metal particles in the cytokinesis-blocked micronucleus test in

human lymphocytes *in vitro*; confirming the unique toxicological properties of the cobalt–tungsten carbide mixture that had initially been demonstrated in cell cytotoxicity assays and animal experiments.

#### *Solubilized cobalt, ROS, and inhibition of DNA repair*

The ability of solubilized cobalt ions to interact with hydrogen peroxide to form ROS to or to inhibit DNA repair processes may contribute to the genotoxic and carcinogenic effects reported for cobalt sulfate and other cobalt compounds (Beyersmann and Hartwig 1992, Lison *et al.* 2001) (see Section 5.4. and Figure 5-2). [Although it is not well presented in the literature, a major target of cobalt ions is the iron-containing dioxygenase enzymes.] Cobalt ions can stabilize hypoxia-inducible factor-1α (HIF-1α) transcription factor, possibly due to cobalt ion inhibition of the prolyl hydroxylase that is responsible for signaling degradation of HIF-1α (Maxwell and Salnikow 2004). This prolyl hydroxylase is a target for cobalt ions where displacement of bound iron at the active site by cobalt inactivates the enzyme. This effect is also found for other dioxygenase enzymes, including the newly discovered histone demethylases, the Alb B type DNA repair enzymes (the human homologue is ABH2), to name but a few. There are data that show inhibition of prolyl hydroxylase by cobalt ions (Kim *et al.* 2006, Hirsilä *et al.* 2005). Dioxygenase enzymes are sensitive to inhibition by nickel, and it has been suggested that cobalt also could inhibit their activity (Davidson *et al.* 2003, Chen and Costa 2009) including cobalt ion inhibition. The effect of their inhibition will stabilize HIF-1α, increase histone methylation which can activate (H3K4) or silence genes (H3K9) and inhibit DNA repair (ABH2). This is a likely mechanism by which cobalt ions exert their carcinogenic and toxic effect in cells. Since these enzymes use ascorbic acid, oxidative stress and depletion of ascorbate is another possible route of inhibition of these enzymes (Salnikow *et al.* 2004). Salnikow *et al.* demonstrated the ability of cobalt to quickly deplete ascorbate, a major cellular antioxidant. This may increase oxidative damage and contribute to deregulation of the expression of HIF-inducible genes. Ascorbate depletion may also impair certain mechanisms of DNA repair (base dealkylation), and nickel ions, which act like cobalt ions, have been shown to inhibit the histone demethylases (Chen *et al.* 2006).

### *5.5.3 Gene expression and apoptosis studies*

Lombaert *et al.* (2008) investigated the *in vitro* expression of genes responsive to hard-metal exposure in human peripheral blood mononucleated cells (PBMC) and monocytes isolated from PBMC. High-density microarrays were used to analyze gene expression profiles after a 24-hour exposure. PBMC and monocytes were exposed in the same medium to 6.0 μg/mL cobalt-equivalent doses of cobalt chloride, metallic cobalt, tungsten carbide, or cobalt–tungsten carbide. Doses were selected based on levels that were previously shown to induce genotoxic effects and apoptosis. The most significantly up-regulated pathways in cobalt–tungsten carbide-treated PBMC included apoptosis regulation and stress/defense response, and the most down-regulated pathway was immune response. For monocytes, the most significantly up- and down-regulated pathways were nucleosome/chromatin assembly and immune response, respectively. Although these data did not identify the specific genes responsible for hard-metal–induced effects, or explain its carcinogenic effects, the results indicated that a large

number of genes associated with cell biology and survival were affected. Furthermore, the similarity of effect of cobalt alone compared with cobalt–tungsten carbide did not indicate mechanisms involved in the unique carcinogenic activity of cobalt–tungsten carbide. Rather, the authors concluded that the critical event was most likely the higher oxidative burst released by cobalt–tungsten carbide compared with cobalt alone.

Lombaert *et al.* (2004) compared the *in vitro* apoptogenic properties of metallic cobalt, cobalt chloride, tungsten carbide, and cobalt–tungsten carbide in human peripheral blood mononucleated cells, lymphocytes, and co-sedimenting monocytes. [Peripheral blood lymphocytes *in vitro* are highly susceptible to chemical-induced apoptosis.] Cells were exposed for 15 minutes, 6 hours, and 24 hours. (Findings on the solubilization of cobalt were reported above). Cobalt–tungsten carbide particles induced apoptosis in cultured human lymphocytes at a dose range (2 to 6 μg/mL cobalt equivalents) previously demonstrated to cause genotoxicity in these cells (Anard *et al.* 1997, Van Goethem *et al.* 1997, De Boeck *et al.* 1998, 2003b). Although tungsten carbide had generally been considered to be biologically inert, Lombaert *et al.* found that tungsten carbide particles in the absence of cobalt also caused apoptosis. At the earlier time points (15 minutes and 6 hours), the mixture did not show an additive response; however, at 24 hours, the apoptotic effect of the mixture was additive and significantly higher than that induced by tungsten carbide or cobalt alone. The induction or modulation of apoptosis by Co(II) ions and other cobalt-containing compounds (reviewed by De Boeck *et al.* 2004) might have some bearing on the mechanism of potential hard-metal carcinogenicity.

### *5.5.4 Other effects of cobalt*

Cobalt ions may mimic or replace other essential divalent metal ions (e.g., magnesium, calcium, iron, copper, or zinc), thus altering many important cellular reactions and functions (NTP 2002a).

A number of mammalian genes (e.g., the genes for metallothionein, heat-shock proteins, and the c-Fos protein) are transcriptionally regulated by a *cis*-acting DNA element in their upstream regions that responds to various metals, including cobalt, to stimulate their expression (Murata *et al.* 1999). These effects are observed *in vitro* at high cobalt concentrations (> 10 μM), but it is unknown whether these phenomena might play a role in pathophysiological processes involved in cobalt carcinogenesis. A similar mechanism is involved in the ability of soluble cobalt (generally cobalt chloride) to induce several tissues and cells to mimic the pathophysiological response to hypoxia (Beyersmann 2002). This response involves various genes, including those coding for erythropoiesis and angiogenesis (Gleadle *et al.* 1995, Steinbrech *et al.* 2000).

In studies designed to explore the molecular mechanisms of gene response to hypoxia, cobalt (as cobalt chloride at a dose of 12 to 60 mg/kg b.w.) upregulated expression of platelet-derived growth factor-B (PDGF-B) in lungs and kidneys of male Sprague-Dawley rats (Bucher *et al.* 1996). Because PDGF is an important growth factor that modulates cell proliferation and the expression of several proto-oncogenes, mainly in mesenchymal cells, this effect of cobalt might explain its fibrogenicity and/or carcinogenicity, but this remains to be documented.

Cobalt also interferes with cellular mechanisms that control the degradation of regulatory proteins such as p53, which is involved in control of the cell cycle, genome maintenance, and apoptosis. It has been reported that in mammalian cells, cobalt (at a concentration of 100 μM) activates HIF-1α, which in turn induces accumulation of p53 through direct association of the two proteins (An *et al.* 1998). Inhibition of proteasome activity in human alveolar macrophages by cobalt (at 100 μM), subsequent accumulation of ubiquitinated proteins, and increased apoptosis have been reported (Araya *et al.* 2002). Whether these biochemical mechanisms are involved in the carcinogenicity observed with some cobalt compounds (including cobalt–tungsten carbide powders and hard metals) remains, however, to be examined.

## 5.6 Summary

### *5.6.1 Absorption, distribution, metabolism, and excretion*

Humans are exposed to cobalt–tungsten carbide hard-metal particles through inhalation and dermal contact. Hard-metal particles usually are of respirable size, suggesting that they potentially are deposited throughout the respiratory tract, including in the alveoli. Studies in humans and animals have demonstrated that when cobalt–tungsten carbide hard-metal particles are deposited in the lung, cobalt metal is rapidly solubilized, cleared from the lung, distributed in the body, and excreted in urine, whereas tungsten carbide particles persist longer in lung tissue. Biomonitoring studies have detected cobalt and tungsten in the urine of workers exposed to cobalt–tungsten carbide powders and hard metal. Cobalt and tungsten also have been detected in whole blood, pubic hair, and toenails, and tungsten has been detected in the feces of hard-metal workers.

### *5.6.2 Toxicity*

Cobalt–tungsten carbide hard-metal dust has been shown to be more toxic than pure cobalt or tungsten carbide in the lungs of rats and *in vitro* in rodent cells (mouse peritoneal macrophages and rat alveolar macrophages) and human cells (type II pneumocytes). Occupational inhalation exposure to cobalt–tungsten carbide hard-metal dust is associated in some workers with the occurrence of hard-metal disease, a giant-cell interstitial pneumonia that can develop into pulmonary fibrosis, with a potentially fatal outcome. Other toxic effects reported in hard-metal workers included contact dermatitis, occupational asthma, and memory loss.

### *5.6.3 Genetic damage and related effects*

Cobalt–tungsten carbide genotoxicity and toxicity may be mediated both by solubilized cobalt ions and through a surface chemistry reaction occurring at the particulate level. Several *in vitro* and *in vivo* studies have demonstrated that a specific reaction results from the interaction between cobalt metal and tungsten carbide particles and oxygen to produce ROS. ROS are involved directly or indirectly (e.g., via a lipoperoxidation process) in the genotoxicity of cobalt–tungsten carbide powders and hard metals. Genotoxicity studies have demonstrated that cobalt–tungsten carbide hard metals cause DNA damage and micronucleus formation in human peripheral blood lymphocytes *in vitro* and in type II pneumocytes (but not peripheral blood lymphocytes) of rats exposed *in vivo*. A study evaluating the genotoxic effects of occupational exposure to cobalt–

tungsten carbide hard-metal particles did not find increased DNA damage or micronucleus formation in blood lymphocytes of exposed workers.

### *5.6.4 Carcinogenicity, toxicity, and genotoxicity of cobalt compounds, alloys, and powder or dust, and tungsten compounds and alloys*

Cobalt and tungsten also occur outside of hard metals in metallic form, including alloys, or as chemical compounds, and these forms also have potential to cause carcinogenic, toxic, or genotoxic effects. Several cobalt compounds (cobalt sulfate, cobalt chloride, and cobalt naphthenate) and cobalt metal have been reported to cause tumors in experimental animals, and cobalt sulfate is listed in the *Report on Carcinogens, Eleventh Edition* as *reasonably anticipated to be a human carcinogen*. The main health effects of concern for hard metals in an occupational setting are respiratory effects, particularly fibrosing alveolitis, but other toxic effects of cobalt include skin allergy, reduced thyroid activity, cardiotoxicity, polycythemia, and reproductive effects. Like other metallic forms, Co(II) compounds are relatively inactive in prokaryotic systems, but genotoxic effects in mammalian cells have been proposed to involve either direct DNA damage through a Fenton-like mechanism with Co(II) ions or an indirect effect through inhibition of repair of DNA damage.

Rats that were treated with intramuscular implants of tungsten alloy pellets containing nickel and cobalt developed rhabdomyosarcomas at the implantation site. Another study reported that tungsten [chemical form not identified] added to the drinking water of rats promoted mammary tumors induced by NMU. No toxicity data were identified for tungsten carbide; however, toxic effects of soluble tungsten compounds include central nervous system disturbances, diarrhea, respiratory failure, and pulmonary edema. Hard-metal workers did not have allergic reactions to sodium tungstate in patch tests. A mixture of tungsten, nickel, and cobalt particles similar to that tested in the carcinogenicity studies increased induction of micronuclei and the number of DNA single-strand breaks in human osteosarcoma cells. The same mixture of metals also induced higher levels of stress genes in human liver carcinoma cell lines compared with the pure metals.

### *5.6.5 Mechanistic studies and considerations*

Cobalt ions can be solubilized from cobalt–tungsten carbide particles (either pre- or post-sintered) in biological media. Tungsten carbide particles do not dissolve but can be phagocytosed by macrophages. While the dissolved cobalt ions and phagocytized tungsten carbide particles could cause genotoxic effects, the surface chemistry of cobalt–tungsten carbide particles might be more important. Cobalt–tungsten carbide hard-metal particles caused significantly more (approximately threefold increased) DNA strand breaks and micronuclei in cultured human lymphocytes than cobalt particles alone, confirming that the cobalt–tungsten carbide mixture has unique toxicological properties. The genotoxicity of cobalt–tungsten carbide particles has been proposed to result from ROS produced at the solid-liquid interface, from ionic cobalt forms dissolved in biological media, or from a combination of both mechanisms. Potential mechanisms for cobalt–tungsten carbide hard-metal carcinogenicity may involve the release of cobalt ions. Cobalt ions have genotoxic effects as evidenced from DNA strand breaks in the

comet assay, inhibition of DNA repair, and micronucleus formation. Cobalt ions also have been shown to modulate apoptosis, regulate genes involved in the response to hypoxia (possibly through inhibition of dioxygenase enzymes), and replace or mimic essential divalent metal ions in proteins regulating cell-cycle control and DNA repair, thus altering cellular reactions.

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# 6 References

1. 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. (Support not reported. Authors affiliated with State University of New York Health Center, NY.)

2. ACGIH. 2001. Documentation for BEI: Cobalt, All Organic Forms, Except Cobalt Oxides. In *Documentation of the Threshold Limit Values and Biological Exposure Indices*. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

3. ACGIH. 2007. *Threshold limit values for chemical substances and physical agents and biological exposure*. American Conference of Governmental Industrial Hygienists.

4. 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): 515-26. (Supported by Koichi Honma [Dokkyo University, Mibu, Tochigi, Japan] and the Hungarian Ministry of Welfare. Authors affiliated with National Institute of Occupational Health, Hungary; Dokkyo Medical University, Japan.)

5. Alcaraz X. 1997. *Determinants of Exposure to Airborne Metals in Washington State Tool Grinding Operations*. Master's Thesis, University of Washington 67 pp. Abstract avaialbe at: http://depts.washington.edu/frcg/content/alcaraz.pdf. (Support not reported. Author affiliated with University of Washington, WA.)

6. Alexandersson R. 1988. Blood and urinary concentrations as estimators of cobalt exposure. *Arch Environ Health* 43(4): 299-303. (Support not reported. Author affiliated with Sundsvall's Hospital and the Royal Institute of Technology, Sweden.)

7. Alexandersson R, Lidums V. 1979. Studies on the effects of exposure to cobalt. VII. Cobalt concentrations in blood and urine as exposure indicators. *Arbete Halsa* 8: 2-23 (as cited in Angerer and Heinrich 1988).

8. An WG, Kanekal M, Simon MC, Maltepe E, Blagosklonny MV, Neckers LM. 1998. Stabilization of wild-type p53 by hypoxia-inducible factor 1α. *Nature* 392(6674): 405-408. (Support not reported. Authors affiliated with National Cancer Institute, MD; University of Chicago, IL.)

9. 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. (Supported by the Federal Services of the Scientific, Technical and Cultural Affairs of the Prime Minister's Service, Belgium. Authors affiliated with Université Catholique de Louvain, Belgique; Vrije Univesiteit Brussel, Belgium.)

10. Andersen O. 1983. Effects of coal combustion products and metal compounds on sister chromatid exchange (SCE) in a macrophagelike cell line. *Environ Health Perspect* 47: 239-53. (Supported by Project Coal, Health, Environment, Statens Vattenfallsverk, Sweden. Author affiliated with Odense University, Denmark.)

11. Angerer J, Heinrich R, Szadkowski D, Lehnert G. 1985. Occupational Exposure to Cobalt Powder and Salts - Biological Monitoring and Health Effects. In *Proceedings of an International Conference on Heavy Metals in the Environment, Athens, September 1985*, vol. 2. Luxembourg: Commisson of the European Community. p. 11-13. (Support and affiliations not reported.)

12. Angerer J, Heinrich R. 1988. Chapter 20: Cobalt. In *Handbook on Toxicity of Inorganic Compounds*. Seiler HG, Sigel H, eds. New York: Marcel Dekker, Inc. p. 251-264. (Support not reported. Authors affiliated with Zentralinstitut für Arbeitsmedizin der Gesundheitsbehörde der Freien und Hansestdat, Germany.)

13. Apostoli P, Porru S, Alessio L. 1994. Urinary cobalt excretion in short time occupational exposure to cobalt powders. *Sci Total Environ* 150(1-3): 129-32. (Support not reported. Authors affiliated with University of Brescia, Italy.)

14. Araya J, Maruyama M, Inoue A, Fujita T, Kawahara J, Sassa K, Hayashi R, Kawagishi Y, Yamashita N, Sugiyama E, Kobayashi M. 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. (Support not reported. Authors affiliated with Toyama Medical and Pharmaceutical University, Japan.)

15. Arlauskas A, Baker RS, Bonin AM, Tandon RK, Crisp PT, Ellis J. 1985. Mutagenicity of metal ions in bacteria. *Environ Res* 36(2): 379-88. (Supported by the Australian Welding Research Association. Authors affiliated with University of Sydney, Australia; University of Wollongong, Australia.)

16. ATSDR. 2003b. *Health Consultation. Fallon Leukemia Cluster Investigation. Fallon, Churchill County, Nevada, Feburary 12, 2003*. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. 172 pp.

17. Azom. 2004. Azom.com. http://www.azom.com. Last accessed: 9/13/04.

18. Barceloux DG. 1999. Cobalt. *J Toxicol Clin Toxicol* 37(2): 201-216. (Support not reported. Author's affiliation not indicated.)

19. Beyersmann D, Hartwig A. 1992. The genetic toxicology of cobalt. *Toxicol Appl Pharmacol* 115(1): 137-145. (Support not reported. Authors affiliated with University of Bremen, Germany.)

20. Beyersmann D. 2002. Effects of carcinogenic metals on gene expression. *Toxicol Lett* 127(1-3): 63-68. (Support not reported. Author affiliated with University of Bremen, Germany.)

21. Beyersmann D, Hartwig A. 2008. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol* 82(8): 493-512. (Support not reported. Authors affiliated with University of Bremen, Germany; Technical University of Berlin, Germany.)

22. Bouchard PR, Black J, Albrecht BA, Kaderly RE, Galante JO, Pauli BU. 1996. Carcinogenicity of CoCrMo (F-75) implants in the rat. *J Biomed Mater Res* 32(1): 37-44. (Supported by the Public Health Service from the National Cancer Institute [B.U.P]. Authors affiliated with Cornell University College of Veterinary Medicine, NY; Clemson University, SC; Atlantic Veterinary College, Canada; The Rush Arthritis and Orthopedic Institute, IL.)

23. Bouros D, Hatzakis K, Labrakis H, Zeibecoglou K. 2002. Association of malignancy with diseases causing interstitial pulmonary changes. *Chest* 121(4): 1278-1289. (Support not reported. Authors affiliated with Medical School University of Crete, Greece.)

24. Brookes K. 2002. Through the looking glass - the rather odd world of hardmetals. *Metal Powder Report* 57(5): 28-29. (Support and author affiliations not reported.)

25. Brookes KJA. 1996. *World Directory and Handbook of Hardmetals and Hard Materials* 6th ed., East Barnet, Hertfordshire, U.K.: International Carbide Data. (Support and author affiliations not reported.)

26. Brookes KJA. 1998. *Hardmetals and Other Hard Materials* 3rd ed., East Barnet, Hertfordshire, UK: International Carbide Data. 220 pp. (Support and author affiliations not reported.)

27. 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. (Support not reported. Authors affiliated with NIEHS; Battelle Pacific Northwest Laboratories, WA.)

28. Bucher M, Sandner P, Wolf K, Kurtz A. 1996. Cobalt but not hypoxia stimulates PDGF gene expression in rats. *Am J Physiol* 271(3 Pt 1): E451-E457. (Supported by the Deutsche Forschungsgemeinschaft. Authors affiliated with Institut für Physiologie der Universität Regensburg, Germany.)

29. Casto BC, Meyers J, DiPaolo JA. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res* 39(1): 193-8. (Supported by the National Cancer Institute. Authors affiliated with BioLabs, Inc., IL; National Cancer Institute, MD.)

30. CCPA. 2008. *Cemented Carbide Producers Association - Members*. Cemented Carbide Producers Association. http://www.ccpa.org/pages/members.html. Accessed 10/6/08.

31. Cereda C, Redaelli ML, Canesi M, Carniti A, Bianchi S. 1994. Widia tool grinding: the importance of primary prevention measures in reducing occupational exposure to cobalt. *Sci Total Environ* 150(1-3): 249-51. (Support not reported. Authors affiliated with Local Health Unit No. 60, Italy.)

32. Chen H, Costa M. 2009. Iron- and 2-oxoglutarate-dependent dioxygenases: an emerging group of molecular targets for nickel toxicity and carcinogenicity. *Biometals* 22(1): 191-6. (Supported by NIEHS. Authors affiliated with New York University School of Medicine, NY.)

33. Chen H, Ke Q, Kluz T, Yan Y, Costa M. 2006. Nickel ions increase histone H3 lysine 9 dimethylation and induce transgene silencing. *Mol Cell Biol* 26(10): 3728-37. (Supported by NIEHS and NCI. Authors affiliated with New York University Medical Center, NY; Northwestern Polytechnical University, China.)

34. Chiappino G. 1994. Hard metal disease: clinical aspects. *Sci Total Environ* 150(1-3): 65-8. (Support not reported. Author affiliated with University of Milan, Italy.)

35. Colognato R, Bonelli A, Ponti J, Farina M, Bergamaschi E, Sabbioni E, Migliore L. 2008. Comparative genotoxicity of cobalt nanoparticles and ions on human peripheral leukocytes *in vitro*. *Mutagenesis* 23(5): 377-82. (Supported by the Italian Ministry of University and Scientific Research. Authors affiliated with University of Pisa, Italy; European Commission, Italy; University of Parma, Italy.)

36. Corrin B, Butcher D, McAnulty BJ, Dubois RM, Black CM, Laurent GJ, Harrison NK. 1994. Immunohistochemical localization of transforming growth factor-$\beta_1$ in the lungs of patients with systemic sclerosis, cryptogenic fibrosing alveolitis and other lung disorders. *Histopathology* 24(2): 145-150. (Supported by the Scleroderma Foundation of the U.S.A. and the Arthritis and Rheumatism Council, U.K. Authors affiliated with National Heart and Lung Institute, U.K; Royal Brompton Hospital, U.K.; Royal Free Hospital, U.K. )

37. Costa M, Heck JD, Robison SH. 1982. Selective phagocytosis of crystalline metal sulfide particles and DNA strand breaks as a mechanism for the induction of cellular transformation. *Cancer Res* 42(7): 2757-63. (Supported by the EPA, NIEHS and the U.S. Department of Energy. Authors affiliated with University of Texas Medical School at Houston, TX.)

38. CRC. 1999. *CRC Handbook of Chemistry and Physics*, Boca Raton, FL: CRC Press. p. 8-112.

39. Cugell DW. 1998. Cobalt-related lung diseases. *Clinical Pulmonary Medicine* 5(3): 158-164. (Support not reported. Author affiliated with NW University Medical School, IL; Northwestern Memorial Hospital, IL.)

40. Davidson T, Salnikow K, Costa M. 2003. Hypoxia inducible factor-1 alpha-independent suppression of aryl hydrocarbon receptor-regulated genes by nickel. *Mol Pharmacol* 64(6): 1485-93. (Supported by NIEHS and NCI. Authors affiliated with New York University School of Medicine, NY.)

41. Davison AG, Haslam PL, Corrin B, Coutts II, Dewar A, Riding WD, Studdy PR, Newman-Taylor AJ. 1983. Interstitial lung disease and asthma in hard-metal workers: bronchoalveolar lavage, ultrastructural, and analytical findings and results of bronchial provocation tests. *Thorax* 38(2): 119-128. (Supported by the Chest, Heart and Stroke Association. Authors affiliated with Brompton Hospital, U.K; Cardiothoracic Institute, U.K.; Bedford General Hospital; Harefield Hospital.)

42. Day GA, Virji MA, Stefaniak AB. 2008. Characterization of exposures among cemented tungsten carbide workers. Part II: Assessment of surface contamination and skin exposures to cobalt, chromium and nickel. *J Expo Sci Environ Epidemiol*: 1-12. (Support not reported. Authors affiliated with NIOSH.)

43. De Boeck M, Lison D, Kirsch-Volders M. 1998. Evaluation of the *in vitro* direct and indirect genotoxic effects of cobalt compounds using the alkaline comet assay. Influence of interdonor and interexperimental variability. *Carcinogenesis* 19(11): 2021-2029. (Supported by the Belgian Federal Office for Scientific, Technical and Cultural Affairs. Authors affiliated with Vrije Universiteit Brussel, Belgium; Université Catholique de Louvain, Belgium.)

44. 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. (Supported by the Belgian Federal Office for Scientific, Technical and Cultural Affairs and the Cobalt Development Institute. Authors affiliated with Vrije Universiteit Brussel, Belgium; Université Catholique de Louvain, Belgium.)

45. De Boeck M, Lombaert N, De Backer S, Finsy R, Lison D, Kirsch-Volders M. 2003a. *In vitro* genotoxic effects of different combinations of cobalt and metallic carbide particles. *Mutagenesis* 18(2): 177-186. (Supported by the Belgian Federal Office for Scientific, Technical and Cultural Affairs. Authors affiliated with Vrije Universiteit Brussel, Belgium; Université Catholique de Louvain, Belgium.)

46. De Boeck M, Hoet P, Lombaert N, Nemery B, Kirsch-Volders M, Lison D. 2003b. *In vivo* genotoxicity of hard metal dust: induction of micronuclei in rat type II epithelial lung cells. *Carcinogenesis* 24(11): 1793-1800. (Supported by the Belgian Federal Offices for Scientific, Technical and Cultural Affairs and the FRSM. Authors affiliated with Vrije Universiteit Brussel, Belgium; Katholieke Universiteit Leuven, Belgium; Université Catholique de Louvain, Belgium.)

47. De Boeck M, Kirsch-Volders M, Lison D. 2003c. Cobalt and antimony: genotoxicity and carcinogenicity. *Mutat Res* 533(1-2): 135-152. (Support not

reported. Authors affiliated with Vrije Universiteit Brussel, Belgium; Université Catholique de Louvain, Belgium.)

48. 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. (Support not reported. Authors affiliated with Vrije Universiteit Brussel, Belgium; Université Catholique de Louvain, Belgium.)

49. Della Torre F, Cassani M, Segale M, Scarpazza G, Pietra R, Sabbioni E. 1990. Trace metal lung diseases: a new fatal case of hard metal pneumoconiosis. *Respiration* 57(4): 248-53. (Support not reported. Authors affiliated with NRCA Casatenovo (Como), Italy; Commission of the European Communities, Italy.)

50. Dooms-Goossens AE, Debusschere KM, Gevers DM, Dupre KM, Degreef HJ, Loncke JP, Snauwaert JE. 1986. Contact dermatitis caused by airborne agents. A review and case reports. *J Am Acad Dermatol* 15(1): 1-10. (Supported by Syntex Laboratories, Inc. Authors affiliated with Universiteit Leuven, Belgium.)

51. Duerksen-Hughes PJ, Yang J, Ozcan O. 1999. p53 induction as a genotoxic test for twenty-five chemicals undergoing *in vivo* carcinogenicity testing. *Environ Health Perspect* 107(10): 805-12. (Supported by the NSF. Authors affiliated with Georgia State University, GA.)

52. 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. (Support not reported. Authors affiliated with the Commission of the European Communities, Italy; Piazza Ospedale Maggiore, Italy. )

53. Egilsson V, Evans IH, Wilkie D. 1979. Toxic and mutagenic effects of carcinogens on the mitochondria of Saccharomyces cerevisiae. *Mol Gen Genet* 174(1): 39-46. (Supported by the Cancer Research Campaign, Ciba-Geigy Ltd., Dr. K. Fjeldsted, the NATO Science Fund and the Science Fund of Iceland. Authors affiliated with University College London, U.K.)

54. Elinder C-G, Friberg L. 1986. Cobalt. In *Handbook on the Toxicology of Metals*. 2nd ed. Friberg L, Nordberg GF, Vouk V, eds. New York: Elsevier Science Publishers B.V. p. 211-232. (Support and author affiliations not reported.)

55. EnvironmentalChemistry.com. 2005. *Periodic Table of Elements: Element Cobalt - Co*. KBLProductions.com. http://environmentalchemistry.com/yogi/periodic/Co.html. Last accessed: 1/12/05.

56. Fairhall LT, Keenan RG, Brinton HP. 1949. Cobalt and the dust environment of the cemented tungsten carbide industry. *Public Health Rep* 64(15): 485-90. (Support not reported. Authors affiliated with Division of Industrial Hygiene, Public Health Service.)

57. Farah SB. 1983. The in vivo effect of cobalt chloride on chromosomes. *Rev Brasil Genet* VI 3: 433-442 (as cited in De Boeck *et al.* 2003c).

58. Fenoglio I, Marta G, Prandi L, Tomatis M, Coluccia S, Fubini B. 2000. The role of mechanochemistry in the pulmonary toxicity caused by particulate minerals. *J Mater Synth Proces* 8(3-4): 145-153. (Supported by the Italian CNR [Consiglio Nazionale delle Ricerche]. Authors affiliated with Università de Torino, Italy.)

59. Fischer T, Rystedt I. 1985. Hand eczema among hard-metal workers. *Am J Ind Med* 8(4-5): 381-94. (Support not reported. Authors affiliated with University Hospital, Sweden; National Board of Occupational Health, Sweden; Karolinska Institute, Sweden.)

60. FR. 2004. National Toxicology Program: Call for public comments on 21 substances, mixtures, and exposure circumstances proposed for listing in the *Report on Carcinogens, Twelfth Edition*. *Fed Regist* 69(97): 28940-28944.

61. Francia C, Bodoardo S, Penazzi N, Corazzari I, Fenoglio I. 2007. Characterization of the electrochemical process responsible for the free radical release in hard metals. *Electrochimica Acta* 52(26): 7438-7443. (Supported by Regione Piemonte, "Ricerca di metalli atti a sostituire il cobalto in metalli duri/compositi diamantati, ondre ridurre la patogenicita delle polveri a livello polmonare" [Bando sulla Ricerca Scientifica Applica]. Authors affiliated with Politecnico di Torino, Dipartimento di Scienze dei Materiali e Ingegneria Chimica, Italy; Universita degli Studi di Torino, Italy.)

62. Frost AE, Keller CA, Brown RW, Noon GP, Short HD, Abraham JL, Pacinda S, Cagle PT. 1993. Giant cell interstitial pneumonitis. Disease recurrence in the transplanted lung. *Am Rev Respir Dis* 148(5): 1401-1404. (Support not reported. Authors affiliated with Baylor College of Medicine, TX; The Methodist Hospital, TX; SUNY Health Science Center, NY.)

63. Fukunaga M, Kurachi Y, Mizuguchi Y. 1982. Action of some metal ions on yeast chromosomes. *Chem Pharm Bull (Tokyo)* 30(8): 3017-9. (Support not reported. Authors affiliated with the University of Occupational and Environmental Health, Japan; School of Nursing and Medical Technology, Japan.)

64. FurnXpert. 2005. *Other Metal Powders*. CompAS Controls, Inc. http://www.furnxpert.com/other_powders.htm. Last accessed: 1/12/05.

65. 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. (Support not reported. Authors affiliated with University of Pavia, Italy; Commission of the European Communities, Italy; Ospedale Riuniti di Bergamo, Italy.)

66. Gleadle JM, Ebert BL, Firth JD, Ratcliffe PJ. 1995. Regulation of angiogenic growth factor expression by hypoxia, transition metals, and chelating agents. *Am J*

*Physiol* 268(6 Pt 1): C1362-C1368. (Supported by the Wellcome Trust. Authors affiliated with the John Radcliffe Hospital, U.K.)

67. 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): 1293-8. (Supported by the National Heart, Blood and Lung Institute and by the Italian Ministry of Education, University and Research. Authors affiliated with the National Institute of Occupational Safety and Prevention, Italy; University of Parma, Italy; University of Brescia, Italy.)

68. Hahtola PA, Järvenpää RE, Lounatmaa K, Mattila JJ, Rantala I, Uitti JA, Sutinen S. 2000. Hard metal alveolitis accompanied by rheumatoid arthritis. *Respiration* 67(2): 209-212. (Support not reported. Authors affiliated with Tampere University Hospital, Finland; University of Helsinki, Finland; Tampere Regional Institute of Occupational Health, Finland; Dy Ars Pathologiae, Inc., Finland.)

69. Hamilton-Koch W, Snyder RD, Lavelle JM. 1986. Metal-induced DNA damage and repair in human diploid fibroblasts and Chinese hamster ovary cells. *Chem Biol Interact* 59(1): 17-28. (Support not reported. Authors affiliated with University of Connecticut, CT; Stauffer Chemical Company, CT.)

70. Harding HE. 1950. Notes on the toxicology of cobalt metal. *Br J Ind Med* 7(2): 76-78. (Supported by the Medical Research Fund of Sheffield University. Author affiliated with Sheffield University.)

71. Hartwig A. 2000. Recent advances in metal carcinogenicity. *Pure Appl Chem* 72(6): 1007-1014. (Supported by the Deutsche Forschungsgemeinschaft. Author affiliated with University of Karlsruhe, Germany. )

72. Hartwig A, Kasten U, Boakye-Dankwa K, Schlopegrell R, Beyersmann D. 1990. Uptake and genotoxicity of micromolar concentrations of cobalt chloride in mammalian cells. *Toxicol Environ Chem* 28: 205-215.

73. 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. (Supported by the Deutsche Forschungsgemeinschaft, Programm Lebensgrundlage Umwelt und ihre Sicherung and the European Union. Authors affiliated with Universität Karlsruhe, Germany; Institut für Strahlenhygiene, Germany; University of Newcastle, U.K.)

74. Hillerdal G, Hartung M. 1983. On cobalt in tissues from hard metal workers. *Int Arch Occup Environ Health* 53(1): 89-90. (Support not reported. Authors affiliated with Academiska Sjukhuset, Sweden; Sozialmedizin der Universität Erlangen-Nürnberg, Germany.)

75. Hirsilä M, Koivunen P, Xu L, Seeley T, Kivirikko KI, Myllyharju J. 2005. Effect of desferrioxamine and metals on the hydroxylases in the oxygen sensing pathway. *FASEB J* 19(10): 1308-10. (Supported by the Health Science Council, the Finnish Centre of Excellence Program, the S. Juselius Foundation and FibroGen, Inc. Authors affiliated with University of Oulu, Finland; FibroGen, Inc., CA.)

76. Hogstedt C, Alexandersson R. 1990. Dödsorsaker hos Hardmetallarbetare. *Arbete och Hälsa* 21: 1-26. ("Causes of Death Among Hard Metal Workers" - English translation prepared by Global Translation Systems; Chapel Hill, NC. (Supported by the Work Environment Fund and the Sandvik Group. Authors affiliated with the Swedish Institute for Work Environment, Sweden; Karolinska Hospital, Sweden; Royal Institute of Technology, Sweden.)

77. Horowitz SF, Fischbein A, Matza D, Rizzo JN, Stern A, Machac J, Solomon SJ. 1988. Evaluation of right and left ventricular function in hard metal workers. *British Journal of Industrial Medicine* 45(11): 742-746. (Supported by Bernard and Josephine Chaus through the Heart Research Foundation and the NIEHS. Authors affiliated with Mount Sinai School of Medicine, NY.)

78. Howie DW, Vernon-Roberts B. 1988. Long-term effects of intraarticular cobalt-chrome alloy wear particles in rats. *J Arthroplasty* 3(4): 327-236. (Supported by the Daws Research Fellowship, Royal Adelaide Hospital, Australian Orthopaedic Association, Royal Australasian College of Surgeons, and the National Health and Medical Research Council. Authors affiliated with Royal Adelaide Hospital, Australia; University of Adelaide, Australia.)

79. HSDB. 2006a. *Hazardous Substances Database. Tungsten Carbide*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search CAS number. Accessed: 1/18/07.

80. HSDB. 2006b. *Hazardous Substances Database. Cobalt*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search CAS number. Accessed: 1/18/07.

81. Hsu W. 2004. Dr. W. Y. Hsu, Kennametal, Inc., Latrobe, PA letter to Dr. C.W. Jameson, National Toxicology Program, Research Triangle Park, NC, July 16, 2004.

82. 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. (Supported by the Commission of the European Communities. Authors affiliated with Catholic University of Louvain, Belgium.)

83. IARC. 1991. *Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer. 544 pp.

84. 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. Lyon, France: International Agency for Research on Cancer. 330 pp.

85. 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): 269-76. (Support not reported. Authors affiliated with Osaka University, Japan.)

86. Imbrogno P, Alborghetti F. 1994. Evaluation and comparison of the levels of occupational exposure to cobalt during dry and/or wet hard metal sharpening. Environmental and biological monitoring. *Sci Total Environ* 150(1-3): 259-262. (Support not reported. Authors affiliated with Local Sanitary Unit 28, Italy.)

87. ITA. 2008. *Subheading 284990: Carbides, Nesoi, Whether or Not Chemically Defined*. International Trade Administration. U.S. Department of Commerce. http://www.ita.doc.gov/td/industry/otea/Trade-Detail/. Accessed 9/24/08.

88. Jordan C, Whitman RD, Harbut M, Tanner B. 1990. Memory deficits in workers suffering from hard metal disease. *Toxicology Letters* 54(2-3): 241-243. (Support not reported. Authors affiliated with Wayne State University, MI; Detroit Receiving Hospital and University Health Center, MI.)

89. Jordan CM, Whitman RD, Harbut M, Tanner B. 1993. Neuropsychological sequelae of hard metal disease. *Archives of Clinical Neuropsychology* 8(4): 309-326. (Supported by Wayne State University and Oberlin College. Authors affiliated with Wayne State University, MI; Center for Occupational and Environmental Medicine, MI; Detroit Receiving Hospital and University Health Center, MI.)

90. Jordan CM, Whitman RD, Harbut M. 1997. Memory deficits and industrial toxicant exposure: a comparative study of hard metal, solvent and asbestos workers. *Int J Neurosci* 90(1-2): 113-28. (Support not reported. Authors affiliated with University of Minnesota Health Center; Wayne State University; Center of Environmental and Occupational Medicine.)

91. Kada T, Kanematsu N. 1978. Reduction of *N*-methyl-*N*-nitro-*N*-nitrosoguanidine-induced mutations by cobalt chloride in *Escherichia coli*. *Proc Jpn Acad* 54B: 234-237. (Supported by the Ministry of Education, the Ministry of Health and Welfare, and the Science and Technology Agency of Japan. Authors affiliated with National Institute of Genetics, Japan; Gifu College of Dentistry, Japan.)

92. Kadiiska MB, Maples KR, Mason RP. 1989. A comparison of cobalt(II) and iron(II) hydroxyl and superoxide free radical formation. *Arch Biochem Biophys* 275(1): 98-111. (Support not reported. Authors affiliated with NIEHS, U.S.A; Bulgarian Academy of Sciences, Bulgaria.)

93. Kalinich JF, Emond CA, Dalton TK, Mog SR, Coleman GD, Kordell JE, Miller AC, McClain DE. 2005. Embedded weapons-grade tungsten alloy shrapnel rapidly induces metastatic high-grade rhabdomyosarcomas in F344 rats. *Environ Health Perspect* 113(6): 729-734. (Supported by the U.S. Army. Authors affiliated with the Armed Forces Radiobiology Research Institute, MD; Walter Reed Army Institute of Research, MD.)

94. Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. *Mutat Res* 77(2): 109-16. (Supported by the Ministry of Welfare, the Ministry of Education, the Science and Technology Agency of Japan, the Takamatsunomiya Cancer Foundation, the Nissan Science Foundation, and the National Institute of Genetics. Authors affiliated with Gifu College of Dentistry, Japan; National Institute of Genetics, Japan.)

95. Kaplun ZS, Mezencewa NW. 1960. Experimentalstudie uber die toxische wirkung von staub bei der erzeugung von sintermetallen. *Journal of Hygiene, Epidemiology, Microbiology and Immunology*(4): 390-399. (Support and affiliations unknown due to foreign language.)

96. Kasprzak KS, Zastawny TH, North SL, Riggs CW, Diwan BA, Rice JM, Dizdaroglu M. 1994. Oxidative DNA base damage in renal, hepatic, and pulmonary chromatin of rats after intraperitoneal injection of cobalt(II) acetate. *Chem Res Toxicol* 7(3): 329-35. (Support not reported. Authors affiliated with NCI; Data Management Services, Inc. MD; Program Resources, Inc./DynCorp, MD; NIST, MD.)

97. 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. (Supported by the Kooperationsbereich Universität/Arbeiterkammer Bremen and by the Deutsche Forschungsgemeinschaft. Authors affiliated with University of Bremen, Germany; Leiden University, Netherlands.)

98. Kawanishi S, Yamamoto K, Inoue S. 1989. Site-specific DNA damage induced by sulfite in the presence of cobalt(II) ion. Role of sulfate radical. *Biochem Pharmacol* 38(20): 3491-3496. (Supported by the Fijiwara Foundation of Kyoto University and the Ministry of Education, Science and Culture of Japan. Authors affiliated with Kyoto University, Japan.)

99. Kazantzis G. 1986. Tungsten. In *Handbook on the Toxicology of Metals*. 2nd ed. Friberg L, Nordberg GF, Vouk V, eds. New York: Elsevier Science Publishers B.V. p. 610-622. (Support and author affiliations not reported.)

100. Keane MJ, Hornsby-Myers JL, Stephens JW, Harrison JC, Myers JR, Wallace WE. 2002. Characterization of hard metal dusts from sintering and detonation coating processes and comparative hydroxyl radical production. *Chem Res Toxicol* 15(8): 1010-1016. (Support not reported. Authors affiliated with NIOSH.)

101. Kelleher P, Pacheco K, Newman LS. 2000. Inorganic dust pneumonias: the metal-related parenchymal disorders. *Environ Health Perspect* 108 Suppl 4: 685-96.

(Support not reported. Authors affiliated with National Jewish Medical and Research Center; University of Colorado, CO.)

102. Kennedy SM, Chan-Yeung M, Lea J, Teschke K. 1995. Maintenance of stellite and tungsten carbide saw tips: respiratory health and exposure-response evaluations. *Occup Environ Med* 52: 185-191. (Support not reported. Authors affiliated with University of British Columbia, Canada.)

103. Kerckaert GA, Brauninger R, LeBoeuf RA, Isfort RJ. 1996a. Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ Health Perspect* 104(Suppl 5): 1075-1084. (Support not reported. Authors affiliated with Proctor & Gamble Co., OH; Corning Hazelton, VA.)

104. Kerckaert GA, LeBoeuf RA, Isfort RJ. 1996b. Use of the Syrian hamster embryo cell transformation assay for determining the carcinogenic potential of heavy metal compounds. *Fundam Appl Toxicol* 34(1): 67-72. (Support not reported. Authors affiliated with Procter & Gamble Company, OH.)

105. Kharab P, Singh I. 1985. Genotoxic effects of potassium dichromate, sodium arsenite, cobalt chloride and lead nitrate in diploid yeast. *Mutat Res* 155(3): 117-20. (Support not reported. Authors affiliated with Haryana Agricultural University, India; Enviro-Bio-Tech Ltd., PA.)

106. Kharab P, Singh I. 1987. Induction of respiratory deficiency in yeast by salts of chromium, arsenic, cobalt and lead. *Indian J Exp Biol* 25(2): 141-2. (Support not reported. Authors affiliated with Haryana Agricultural University, India; Enviro-Bio-Tech Ltd., PA.)

107. Kim KS, Rajagopal V, Gonsalves C, Johnson C, Kalra VK. 2006. A novel role of hypoxia-inducible factor in cobalt chloride- and hypoxia-mediated expression of IL-8 chemokine in human endothelial cells. *J Immunol* 177(10): 7211-24. (Supported by NIH. Authors affiliated with University of Southern California, CA.)

108. Kirk-Othmer. 1997. *Kirk-Othmer Encyclopedia of Chemical Technology*, New York, NY: Jon Wiley and Sons.

109. Kitamura H, Yoshimura Y, Tozawa T, Koshi K. 1980. Effects of cemented tungsten carbide dust on rat lungs following intratracheal injection of saline suspension. *Acta Pathol Jpn* 30(2): 241-53. (Support not reported. Authors affiliated with Yokahama City University School of Medicine, Japan; National Institute of Industrial Health.)

110. Koponen M, Gustafsson T, Kalliomaki PL. 1982. Cobalt in hard metal manufacturing dusts. *American Industrial Hygiene Association Journal* 43(9): 645-651. (Support not reported. Authors affiliated with Outokumpu Oy, Finland; Institute of Occupational Health, Finland.)

111. 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. (Support not reported. Authors affiliated with University of Erlangen-Nürnberg, Germany; Institute for Ecological Chemistry, Germany.)

112. Kriz R. 2004. *Sintering of a Powder Compact*. Virginia Tech. http://www.sv.vt.edu/classes/MSE2034_NoteBook/MSE2034_kriz_NoteBook/diffusion/apps/sinter.html. Last accessed: 1/25/05.

113. Kumagai S, Kusaka Y, Goto S. 1996. Cobalt exposure level and variability in the hard metal industry of Japan. *Am Ind Hyg Assoc J* 57(4): 365-369. (Support not reported. Authors affiliated with Osaka Prefectural Institute of Public Health, Japan; Fukui Medical School, Japan; Osaka Prefectural Center for Workers, Japan.)

114. Kusaka Y, Yokoyama K, Sera Y, Yamamoto S, Sone S, Kyono H, Shirakawa T, Goto S. 1986b. Respiratory diseases in hard metal workers: an occupational hygiene study in a factory. *Br J Ind Med* 43(7): 474-485. (Support not reported. Authors affiliated with Osaka University, Japan; National Kinki Chuo Hospital for Chest Diseases, Japan; National Institute for Industrial Health, Japan.)

115. Kusaka Y, Kumagai S, Kyono H, Kohyama N, Shirakawa T. 1992. Determination of exposure to cobalt and nickel in the atmosphere in the hard metal-industry. *Ann Occup Hyg* 36(5): 497-507. (Support not reported.Authors affiliated with Jichi Medical School, Japan; Osaka Prefectual Institute of Public Health, Japan; National Institute of Industrial Health, Japan; Osaka University, Japan.)

116. Kusaka Y. 1996. Cobalt and nickel induced hard metal asthma. *Toxicol Metals*: 461-468. (Support and author affiliations not reported.)

117. Lasfargues G, Lison D, Maldague P, Lauwerys R. 1992. Comparative study of the acute lung toxicity of pure cobalt powder and cobalt-tungsten carbide mixture in rat. *Toxicol Appl Pharmacol* 112(1): 41-50. (Supported by the Fondation Ernest Duffo (France) and the Fonds de la Recherche Scientifique Médicale (Belgium). Authors affiliated with Catholic University of Louvain, Belgium)

118. 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. (Supported by the "Caisse Régionale d'Assurance Maladie de la Region Centre." Authors affiliated with Hôpital Bretonneau, France; Institut National de Recherche et de Sécurité, France.)

119. 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. (Supported by the Commission of the European Communities and the Fonds de la Recherche Scientifique Médicale, Belgium. Authors affiliated with Catholic University of Louvain, Belgium; University Hospital of Mont Godinne, Belgium.)

120. Lechleitner P, Defregger M, Lhotta K, Totsch M, Fend F. 1993. Goodpasture's syndrome: Unusual presentation after exposure to hard metal dust. *Chest* 103(3): 956-957. (Support not reported. Authors affiliated with Med Universitatsklinik, Austria; Innsbruck University Hospital, Austria.)

121. Leggett RW. 1997. A model of the distribution and retention of tungsten in the human body. *Sci Total Environ* 206(2-3): 147-65. (Support not reported. Author affiliated with Oak Ridge National Laboratory, TN.)

122. Leonard S, Gannett PM, Rojanasakul Y, Schwegler-Berry D, Castranova V, Vallyathan V, Shi X. 1998. Cobalt-mediated generation of reactive oxygen species and its possible mechanism. *J Inorg Biochem* 70(3-4): 239-244. (Support not reported. Authors affiliated with NIOSH; West Virginia University, WV.)

123. Lewis CG, Belniak RM, Plowman MC, Hopfer SM, Knight JA, Sunderman FW, Jr. 1995. Intraarticular carcinogenesis bioassays of CoCrMo and TiAlV alloys in rats. *J Arthroplasty* 10(1): 75-82. (Supported by the American Cancer Society and the Northeast Utilities Company. Authors affiliated with University of Connecticut Medical School, CT; University of Utah Medical School, UT.)

124. Lewis CG, Sunderman FW, Jr. 1996. Metal carcinogenesis in total joint arthroplasty: Animal models. *Clin Orthop* 1(329S): S264-S268. (Support not reported. Authors affiliated with University of Connecticut Health Center, CT.)

125. Lichtenstein ME, Bartl F, Pierce RT. 1975. Control of cobalt exposures during wet process tungsten carbide grinding. *Am Ind Hyg Assoc J* 36(12): 879-885. (Support not reported. Authors affiliated with The Boeing Company, WA; W.A. Botting Company, WA.)

126. Lindegren CC, Nagai S, Nagai H. 1958. Induction of respiratory deficiency in yeast by manganese, copper, cobalt and nickel. *Nature* 182(4633): 446-8. (Supported by the American Cancer Society. Authors affiliated with Southern Illinois University, IL.)

127. Linna A, Oksa P, Palmroos P, Roto P, Laippala P, Uitti J. 2003. Respiratory health of cobalt production workers. *Am J Ind Med* 44(2): 124-32. (Supported by the Finnish Work Environment Fund. Authors affiliated with Outokumpu Zinc Oy, Finland; Tampere University Hospital, Finland, University of Tampere, Finland.)

128. Linnainmaa M. 1995. Control of exposure to cobalt during grinding of hard metal blades. *Appl Occup Environ Hyg* 10(8): 692-697. (Supported by the Finnish Work Environment Fund. Author affiliated with Kuopio Regional Institute of Occupational Health, Finland.)

129. Linnainmaa M, Kangas J, Kalliokoski P. 1996. Exposure to airborne metals in the manufacture and maintenance of hard metal and stellite blades. *Am Ind Hyg Assoc J* 57(2): 196-201. (Supported by the Finnish Work Environment Fund and the Occupational Health and Safety Inspectorate of Central Finland. Authors affiliated

with Finnish Institute of Occupational Health, Finland; University of Kuopio, Finland.)

130. 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. (Supported by the Finnish Work Environment Fund. Authors affiliated with Finnish Institute of Occupational Health, Finland.)

131. Linnainmaa M, Susitaival P, Mäkelä E, Sjöblom T. 1997. Respiratory symptoms and dermatoses among grinders and brazers of hard metal and stellite blades. *Occupational Medicine* 47(1): 33-39. (Supported by the Finnish Work Environment Fund. Authors affilated with Finnish Institute of Occupational Health, Finland; Enso Co., Finland.)

132. Lison D, Lauwerys R. 1990. *In vitro* cytotoxic effects of cobalt-containing dusts on mouse peritoneal and rat alveolar macrophages. *Environ Res* 52(2): 187-198. (Support not reported. Authors affiliated with Catholic University of Louvain, Belgium.)

133. 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. (Support not reported. Authors affiliated with Catholic University of Louvain, Belgium.)

134. 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. (Supported by the Johns Hopkins Center for Alternative to Animal Testing. Authors affiliated with Catholic University of Louvain, Belgium.)

135. Lison D, Lauwerys R. 1995. The interaction of cobalt metal with different carbides and other mineral particles on mouse peritoneal macrophages. *Toxicology In Vitro* 9(3): 341-347. (Support not reported. Authors affiliated with Catholic University of Louvain, Belgium.)

136. 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. (Support not reported. Authors affiliated with Catholic University of Louvain, Belgium.)

137. 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. (Support not reported. Authors affiliated with Catholic University of Louvain, Belgium.)

138. 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. (Supported by the Commission of the European Communities and the Fonds de la Recherche

Scientifique Médicale, Belgium. Authors affiliated with Catholic University of Louvain, Belgium; University of Torino, Italy.)

139. 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. (Support not reported. Author affiliated with Catholic University of Louvain, Belgium)

140. 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. (Supported by the Commission of the European Communities, the Belgian Funds for Scientific Research and the Federal Services of the Scientific, Technical and Cultural Affairs of the Prime Minister's Services. Authors affiliated with Catholic University of Louvain, Belgium; Laboratorium voor Pneumologie, Belgium.)

141. Lison D. 2000. Toxicity of cobalt-containing dusts. *Toxicol Appl Pharmacol* 168(2): 173 (Letter to the editor). (Support not reported. Author affiliated with Catholic University of Louvain, Belgium)

142. Lison D, De Boeck M, Verougstraete V, Kirsch-Volders M. 2001. Update on the genotoxicity and carcinogenicity of cobalt compounds. *Occup Environ Med* 58(10): 619-625. (Support not reported. Authors affiliated with Universite Catholique de Louvain, Belgium; Vrije Universiteit Brussel, Belgium.)

143. 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. (Supported by the Belgian Federal Offices for Scientific, Technical and Cultural Affairs. Authors affiliated with Catholic University of Louvain, Belgium; C.N.R, Italy; Vrije Universiteit Brussel, Belgium.)

144. 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. *Toxicology and Applied Pharmacology* 227: 299-312. (Supported by a VUB fund. Authors affiliated with Vrije Universiteit Brussel, Belgium; Universite catholique de Louvain, Belgium; VIB MicroArray Facility, Belgium.)

145. Mao Y, Liu KJ, Jiang JJ, Shi X. 1996. Generation of reactive oxygen species by Co(II) from $H_2O_2$ in the presence of chelators in relation to DNA damage and 2'-deoxyguanosine hydroxylation. *J Toxicol Environ Health* 47(1): 61-75. (Support not reported. Authors affiliated with NCI; Dartmouth Medical School, NH.)

146. 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. (Supported by the Belgian Offices for Scientific, Technical, and Cultural Affairs of the Prime Minister's Office and the EU Cancer Risk Biomarkers Project. Authors

affiliated with Vrije Universiteit Brussel, Belgium; Catholic University of Louvain, Belgium.)

147. Maxwell P, Salnikow K. 2004. HIF-1: an oxygen and metal responsive transcription factor. *Cancer Biol Ther* 3(1): 29-35. (Support not reported. Authors affiliated with Imperial College, UK; NCI.)

148. McDermott FT. 1971. Dust in the cemented carbide industry. *Am Ind Hyg Assoc J* 32(3): 188-93. (Support not reported. Author affiliated with Michigan Department of Public Health.)

149. McLean JR, McWilliams RS, Kaplan JG, Birnboim HC. 1982. Rapid detection of DNA strand breaks in human peripheral blood cells and animal organs following treatment with physical and chemical agents. *Prog Mutat Res* 3: 137-141. (Support not reported. Authors affiliated with Radiation Protection Bureau, Canada; University of Ottawa, Canada; Chalk River Nuclear Laboratories, Canada.)

150. Meyer-Bisch C, Pham QT, Mur JM, Massin N, Moulin JJ, Teculescu D, Carton B, Pierre F, Baruthio F. 1989. Respiratory hazards in hard metal workers: a cross sectional study. *Br J Ind Med* 46(5): 302-309. (Support not reported. Authors affiliated with INRS, France; INSERM, France.)

151. Miller AC, Mog S, McKinney L, Luo L, Allen J, Xu J, Page N. 2001. Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy metal-tungsten alloy particles: induction of genotoxic effects. *Carcinogenesis* 22(1): 115-125. (Supported by the Armed Forces Radiobiology Research Institute. Authors affiliated with Armed Forces Radiobiology Research Institute, MD; NCI, MD.)

152. Miller AC, Xu J, Stewart M, Prasanna PG, Page N. 2002. Potential late health effects of depleted uranium and tungsten used in armor-piercing munitions: comparison of neoplastic transformation and genotoxicity with the known carcinogen nickel. *Mil Med* 167(2 Suppl): 120-122. (Supported by the Armed Forces Radiobiology Research Institute. Authors affiliated with the Armed Forces Radiobiology Research Institute, MD.)

153. Miller AC, Brooks K, Smith J, Page N. 2004. Effect of the militarily-relevant heavy metals, depleted uranium and heavy metal tungsten-alloy on gene expression in human liver carcinoma cells (HepG2). *Mol Cell Biochem* 255(1-2): 247-56. (Supported by Armed Forces Radiobiology Research Institute. Authors affiliated with Armed Forces Radiobiology Research Institute, MD; NCI.)

154. Miyaki M, Akamatsu N, Ono T, Koyama H. 1979. Mutagenicity of metal cations in cultured cells from Chinese hamster. *Mutat Res* 68(3): 259-63. (Support not reported. Authors affiliated with the Tokyo Metropolitan Institute of Medical Science, Japan; Japanese Foundation for Cancer Research, Japan.)

155. Mochizuki H, Kada T. 1982. Antimutagenic action of cobaltous chloride on Trp-P-1-induced mutations in Salmonella typhimurium TA98 and TA1538. *Mutat Res*

95(2-3): 145-57. (Supported by the Ministry of Education, the Ministry of Health and Welfare, the Nissan Foundation and the National Institute of Genetics. Authors affiliated with the National Institute of Genetics, Japan.)

156. Moriyama H, Kobayashi M, Takada T, Shimizu T, Terada M, Narita JI, Maruyama M, Watanabe K, Suzuki E, Gejyo F. 2007. Two-dimensional analysis of elements and mononuclear cells in hard metal lung disease. *American Journal of Respiratory and Critical Care Medicine* 176(1): 70-77. (Supported by a Grant-in-Aid for Scientific Research. Authors affiliated with Niigata University, Japan; JA Niigata Kouseiren Uonuma Hospital, Japan.)

157. Mosconi G, Bacis M, Leghissa P, Maccarana G, Arsuffi E, Imbrogno P, Airoldi L, Caironi M, Ravasio G, Parigi PC, Polini S, Luzzana G. 1994. Occupational exposure to metallic cobalt in the Province of Bergamo. Results of a 1991 survey. *Sci Total Environ* 150(1-3): 121-8. (Support not reported. Authors affiliated with Ospedali Riuniti of Bergamo, Italy; Local Sanitary Units 26-32, Italy.)

158. Moulin JJ, Wild P, Mur JM, Fournier-Betz M, Mercier-Gallay M. 1993b. A mortality study of cobalt production workers: an extension of the follow-up. *Am J Ind Med* 23(2): 281-288. (Support not reported. Authors affiliated with INRS, France.)

159. Moulin JJ, Romazini S, Lasfargues G, Peltier A, Bozec C, Deguerry P, Pellet F, Wild P, Perdrix A. 1997. [Development of a job-exposure matrix in the French hard metal industry]. *Rev Epidemiol Sante Publique* 45(1): 41-51. (Support not reported. Authors affiliated with INRS, France; Hôpital A. Michallon, Hôpital Bretonneau; ERAMET, France; Sandvik Hard Metals.)

160. 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. (Support not reported. Authors affiliated with INRS, France; Hôpital A, Michallon, France; Hôpital Bretonneau, France; Eramet, France; Sandvik Hard Metals, France.)

161. MPR. 2002. *Metal Powder Report - April News*. Elsevier Advanced Technology. http://www.metal-powder.net/april02news.html. Last accessed: 9/13/04.

162. Mur JM, Moulin JJ, Charruyer-Seinerra MP, Lafitte J. 1987. A cohort mortality study among cobalt and sodium workers in an electrochemical plant. *Am J Ind Med* 11(1): 75-81. (Support not reported. Authors affiliated with INRS, France.)

163. 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. (Support not reported. Authors affiliated with National Institute of Industrial Health, Japan.)

164. Mutti A, Corradi M. 2006. Recent developments in human biomonitoring: non-invasive assessment of target tissue dose and effects of pneumotoxic metals. *Med*

*Lav* 97(2): 199-206. (Supported by the National Heart, Blood and Lung Institute, Bethesda, MD. Authors affiliated with University of Parma, Italy.)

165. 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. (Supported by the U.S. Department of Energy, the South African Medical Research Council, the National Science Foundation, the Medical Research Council, U.K. and the Arthritis and Rheumatism Council, U.K. Authors affiliated with National Institute of Standards and Technology, MD; University of Stellenbosch, South Africa; University of Maryland, MD; NCI, MD; University of California, CA. )

166. Nemery B, Hoet P. 2000. Reply to letter to editor. *Toxicol Appl Pharmacol* 168(2): 173-174. (Support not reported. Authors affiliated with the Laboratory of Pneumology, Belgium.)

167. Nemery B, Verbeken EK, Demedts M. 2001. Giant cell interstitial pneumonia (hard metal lung disease, cobalt lung). *Seminars in Respiratory and Critical Care Medicine* 22(4): 435-447. (Support not reported. Authors affiliated with Laboratorium voor Pneumologie, Belgium; U.Z. Leuvan, Belgium.)

168. 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): 73-7. (Supported by the Commission of the European Communities. Authors affiliated with the Commission of the European Communties, Italy; Ospedali Riuniti di Bergamo, Italy.)

169. NIEHS. 2002. *Cobalt Dust (7440-48-4): Review of Toxicological Literature*. Research Triangle Park, NC: National Institute of Environmental Health Sciences. 53 pp.

170. NIOSH. 1977. *Criteria for a Recommended Standard. Occupational Exposure to Tungsten and Cemented Tungsten Carbide*. Washington, D.C: National Institute of Health, Education and Welfare. http://www.cdc.gov/niosh/77-127.html.

171. NIOSH. 1981. *Occupational Hazard Assessment: Criteria for Controlling Occupational Exposure to Cobalt*. DHHS (NIOSH) Publication No. 82-107 Washington, D.C.: National Institute for Occupational Safety and Health. 35 pp. http://www.cdc.gov/niosh/82-107.html.

172. NIOSH. 1987a. *Health Hazard Evaluation Report: GTE/Valenite Corporation, Westminster, South Carolina*. HETA 85-064-1844. U.S. Department of Health and Human Services, National Institute for Occupational Health and Safety.

173. NIOSH. 1987b. *Health Hazard Evaluation Report: Eccles Saw and Tool Company, Cincinnati, Ohio*. HETA 85-415-1806. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. 21 pp.

174. NIOSH. 1987c. *Health Hazard Evaluation Report: Eccles Saw and Tool Company, Cincinnati, Ohio*. HETA 85-415-1806. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. 21 pp.

175. NIOSH. 1988. *Health Hazard Evaluation Report:General Electric Company*. HETA 85-423-1904. U.S. Department of Health and Human Services, National Institute for Occupational Health and Safety.

176. Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. *Mutat Res* 31(3): 185-9. (Support not reported. Author affiliated with Doshisha University, Japan.)

177. Nordberg G. 1994. Assessment of risks in occupational cobalt exposures. *Sci Total Environ* 150(1-3): 201-7. (Support not reported. Author affiliated with Umea University, Sweden.)

178. NTP. 1998. *Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate in F344/N Rats and B6C3F1 Mice*. Technical Report Series No. 471. NIH Publication No. 98-3961. Research Triangle Park, NC: National Toxicology Program. 268 pp. http://ntp-server.niehs.nih.gov/htdocs/LT_rpts/tr471.pdf.

179. NTP. 2002a. *Report on Carcinogens Background Document for Cobalt Sulfate*. National Toxicology Program. http://ntp-server.niehs.nih.gov/newhomeroc/roc11/CoSO4Pub.pdf.

180. NTP. 2002b. *Cobalt Dust [7440-48-4]: Review of Toxicological Literature*. Research Triangle Park, NC: National Institute of Environmental Health Sciences. http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPdf/CobaltDust.pdf.

181. NVDHSS. 2008. *Polonium-210 Information Sheet*. Carson City, NV: State of Nevada, Department of Health and Human Services. 3 pp. http://health.nv.gov/docs/po210.pdf.

182. O'Brien W. 1996. *Biomaterials Properties Database: Mohs' Hardness*. Quintessence Publishing. http://www.lib.umich.edu/dentlib/Dental_tables/Mohshard.html. Last accessed: 1/25/05.

183. Ogawa HI, Sakata K, Inouye T, Jyosui S, Niyitani Y, Kakimoto K, Morishita M, Tsuruta S, Kato Y. 1986. Combined mutagenicity of cobalt(II) salt and heteroaromatic compounds in Salmonella typhimurium. *Mutat Res* 172(2): 97-104. (Supported by the Fukuoka Cancer Association and Meisen-kai. Authors affiliated with Kyushu Institute of Technology, Japan; Kitakyushu Municipal Institute for Environmental Health Sciences, Japan; Kitakyushu Research Center for Protection of Environmental Pollution, Japan.)

184. Ohori NP, Sciurba FC, Owens GR, Hodgson MJ, Yousem SA. 1989. Giant-cell interstitial pneumonia and hard-metal pneumoconiosis. A clinicopathologic study of four cases and review of the literature. *Am J Surg Pathol* 13(7): 581-7. (Supported by the Pathology Education and Research Foundation. Authors affiliated with University of Pittsburgh School of Medicine, PA. )

185. Olivero S, Villani P, Botta A. 1995. Genotoxic effects of cobalt chloride, sulfate and nitrate on cultured human lymphocytes. *Med Sci Res* 23: 339-341. (Support not reported. Authors affiliated with Laboratoire de Toxicologie Fondamentale-Ergotoxicologie, France.)

186. Painter RB, Howard R. 1982. The Hela DNA-synthesis inhibition test as a rapid screen for mutagenic carcinogens. *Mutat Res* 92(1-2): 427-37. (Supported by the U.S. Department of Energy. Authors affiliated with University of California, CA.)

187. Palit S, Sharma A, Taluker G. 1991. Chromosomal aberrations induced by cobaltous chloride in mice in vivo. *Biol Trace Elem Res* 29(2): 139-145 (as cited in De Boeck *et al.* 2003c).

188. Paton GR, Allison AC. 1972. Chromosome damage in human cell cultures induced by metal salts. *Mutat Res* 16(3): 332-6. (Support not reported. Authors affiliated with the Clinical Research Center, U.K.)

189. Paulsen LP, Kilens G. 1994. Engineering and work practice controls in the tungsten carbide tooling industry to control airborne cobalt dust exposure. *Appl Occup Environ Hyg* 9(2): 106-108. (Support not reported. Authors affiliated with OSHA.)

190. 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).

191. Peltola P, Wikstrom E. 2006. Tyre stud derived tungsten carbide particles in urban street dust. *Boreal Environ Res* 11(3): 161-168. (Supported by Heikki Salakari, Turvanasta Oy, the Äspö Research School and The Knowledge Foundation. Authors affiliated with the Department of Biology and Environmental Sciences, Sweden; Golder Associates, Sweden.)

192. Persson E, Henriksson J, Tjalve H. 2003. Uptake of cobalt from the nasal mucosa into the brain via olfactory pathways in rats. *Toxicol Lett* 145(1): 19-27. (Supported by the Swedish Council for Working Life and Social Research and the Foundation for Strategic Environmental Research. Authors affiliated with Swedish University of Agricultural Sciences, Sweden.)

193. Posma FD, Dijstelberger SK. 1985. Serum and urinary cobalt levels as indicators of cobalt exposure in hard metal workers. *Heavy Metals in the Environment, Int Conf 5th* 2(89-91). (Support not reported. Authors affiliated with Princess Irene Hospital, Netherlands; Occupational Health Center, Netherlands.)

194. Potolicchio I, Mosconi G, Forni A, Nemery B, Seghizzi P, Sorrentino R. 1997. Susceptibility to hard metal lung disease is strongly associated with the presence of glutamate 69 in HLA-DP beta chain. *Eur J Immunol* 27(10): 2741-3. (Supported by the European Economic Community and CNR. Authors affiliated with University of Rome La Sapienza, Italy; CNR, Italy; Ospedali Riuniti Bergamo, Italy; University of Milano, Italy; Katholieke Universiteit Leuven, Belgium; University L'Aquila, Italy.)

195. Potolicchio I, Festucci A, Hausler P, Sorrentino R. 1999. HLA-DP molecules bind cobalt: a possible explanation for the genetic association with hard metal disease. *Eur J Immunol* 29(7): 2140-7. (Supported by the CNR. Authors affiliated with University La Sapienza, Italy; CNR, Italy.)

196. Prazmo W, Balbin E, Baranowska H, Ejchart A, Putrament A. 1975. Manganese mutagenesis in yeast. II. Conditions of induction and characteristics of mitochondrial respiratory deficient Saccharomyces cerevisiae mutants induced with manganese and cobalt. *Genet Res* 26(1): 21-9. (Supported by the Polish Academy of Sciences. Authors affiliated with the Polish Academy of Sciences, Poland.)

197. Putrament A, Baranowska H, Ejchart A, Jachymczyk W. 1977. Manganese mutagenesis in yeast. VI. Mn2+ uptake, mitDNA replication and ER induction: comparison with other divalent cations. *Mol Gen Genet* 151(1): 69-76. (Supported by the Polish Academy of Sciences and the PHS. Authors affiliated with the Polish Academy of Sciences, Poland.)

198. Rengasamy A, Kommineni C, Jones JA, Fedan JS. 1999. Effects of hard metal on nitric oxide pathways and airway reactivity to methacholine in rat lungs. *Toxicol Appl Pharmacol* 157(3): 178-191. (Support not reported. Authors affiliated with NIOSH.)

199. Resende de Souza-Nazareth H. 1976. Efeito do cloreto de cobalto em ao-disjuncao. *Ceince e Cultura* 28(12): 1472-1475 (as cited in De Boeck *et al.* 2003c).

200. 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. (Support not reported. Authors affiliated with Niguarda Hospital, Italy; Commission of the European Communities, Italy.)

201. Rizzato G, Fraioli P, Sabbioni E, Pietra R, Barberis M. 1992. Multi-element follow up in biological specimens of hard metal pneumoconiosis. *Sarcoidosis* 9(2): 104-17. (Support not reported. Authors affiliated with Niguarda Hospita, Italy; Commission of the European Communities, Italy.)

202. Robison SH, Cantoni O, Costa M. 1982. Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. *Carcinogenesis* 3(6): 657-62. (Supported by the U.S. EPA, the U.S. Department of Energy and NCI. Authors affiliated with the University of Texas Medical School at Houston, TX.)

203. Roesems G, Hoet PH, Demedts M, Nemery B. 1997. *In vitro* toxicity of cobalt and hard metal dust in rat and human type II pneumocytes. *Pharmacol Toxicol* 81(2): 74-80. (Supported by the DWTC and the European Community. Authors affiliated with K.U. Leuven, Belgium.)

204. Roesems G, Hoet PH, Dinsdale D, Demedts M, Nemery B. 2000. *In vitro* cytotoxicity of various forms of cobalt for rat alveolar macrophages and type II pneumocytes. *Toxicol Appl Pharmacol* 162(1): 2-9. (Supported by DWTC and the European Community. Authors affiliated with K.U. Leuven, Belgium; MRC Toxicology Unit, UK.)

205. Rolfe MW, Paine R, Davenport RB, Strieter RM. 1992. Hard metal pneumoconiosis and the association of tumor necrosis factor-alpha. *Am Rev Respir Dis* 146(6): 1600-1602. (Supported by NIH and the American Lung Association. Authors affiliated with University of Michigan, MI; R. J. R. Nabisco.)

206. Rossman TG. 1981. Effect of metals on mutagenesis and DNA repair. *Environ Health Perspect* 40: 189-195. (Support not reported. Author affiliated with New York University School of Medicine, NY.)

207. Rossman TG, Molina M, Meyer LW. 1984. The genetic toxicology of metal compounds: I. Induction of lambda prophage in E coli WP2s(lambda). *Environ Mutagen* 6(1): 59-69. (Supported by NCI, DHHS and NIEHS. Authors affiliated with New York University Medical Center, NY.)

208. Rubin CS, Holmes AK, Belson MG, Jones RL, Flanders WD, Kieszak SM, Osterloh J, Luber GE, Blount BC, Barr DB, Steinberg KK, Satten GA, McGeehin MA, Todd RL. 2007. Investigating childhood leukemia in Churchill County, Nevada. *Environ Health Perspect* 115(1): 151-7. (Support not reported. Authors affiliated with CDC; Nevada State Health Division, NV.)

209. Ruediger HW. 2000. Hard metal particles and lung disease: coincidence or causality? *Respiration* 67(2): 137-8. (Support not reported. Author affiliated with University of Vienna, Austria.)

210. Rüttner JR, Spycher MA, Stolkin I. 1987. Inorganic particulates in pneumoconiotic lungs of hard metal grinders. *Br J Ind Med* 44(10): 657-660. (Support not reported. Authors affiliated with University Hospital of Zürich, Switzerland; Zürich Pneumoconiosis Research Group, Switzerland.)

211. 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. (Support not reported. Authors affiliated with European Commission, Italy; Fondazione Clinica del Lavoro, Italy; Ospedali Riuniti di Bergamo, Italy; University of Milan, Italy; University of Turin, Italy.)

212. 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. (Support not reported. Authors affiliated with European Commission, Italy; Ospedali Riuniti di Bergamo, Italy; Fondazione Clinica del Lavoro, Italy.)

213. Sahle W. 1992. Possible role of tungsten oxide whiskers in hard-metal pneumoconiosis. *Chest* 102(4): 1310. (Supported by the Swedish Work Environment Fund. Author affiliated with National Institute of Occupational Health, Sweden.)

214. Sahle W, Laszlo I, Krantz S, Christensson B. 1994. Airborne tungsten oxide whiskers in a hard-metal industry. Prelimary findings. *Ann Occup Hyg* 38(1): 37-44. (Supported by the Swedish work Environmental Fund. Authors affiliated with National Institute of Occupational Health, Sweden.)

215. Sahle W, Krantz S, Christensson B, Laszlo I. 1996. Preliminary data on hard metal workers exposure to tungsten oxide fibres. *Sci Total Environ* 191(1-2): 153-167. (Supported by the Swedish Council for Working Life Research. Authors affiliated with National Institute for Working Life, Sweden.)

216. Sala C, Mosconi G, Bacis M, Bernabeo F, Bay A, Sala O. 1994. Cobalt exposure in 'hard metal' and diamonds grinding tools manufacturing and in grinding processes. *Sci Total Environ* 150(1-3): 111-6. (Support not reported. Authors affiliated with USL, Italy; Ospedali Riuniti di Bergamo, Italy; Ospedale di Desio, Italy; Department of Safety and Hygiene, Italy.)

217. Salnikow K, Donald SP, Bruick RK, Zhitkovich A, Phang JM, Kasprzak KS. 2004. Depletion of intracellular ascorbate by the carcinogenic metals nickel and cobalt results in the induction of hypoxic stress. *J Biol Chem* 279(39): 40337-44. (Supported by NIEHS, Burroughs Wellcome Fund and University of Texas. Authors affiliated with NIH; University of Texas, TX; Brown University, RI.)

218. 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. (Support not reported. Authors affiliated with Università di Torino, Italy; Sandwick SpA, Italy.)

219. 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. (Support not reported. Authors affiliated with Universita di Torino, Italy; USL, Italy.)

220. 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. (Support not reported. Authors affiliated with Università di Torino, Italy.)

221. Schell J, Pardus M. 2008. Tungsten and cobalt in Fallon, Nevada: association with childhood leukemia. *Environ Health Perspect* 116(5): A196-7; author reply A197. (Support not reported. Authors affiliated with Kennametal, Inc., NV; ENTRIX Inc., TX; Arcadis-BBL, PA.)

222. Schepers GW. 1955a. The biological action of particulate cobalt metal; studies on experimental pulmonary histopathology. *AMA Arch Ind Health* 12(2): 127-133. (Support not reported. Author affiliated with Saranac Laboratory, NY.)

223. Schepers GW. 1955b. The biological action of tungsten carbide and cobalt; studies on experimental pulmonary histopathology. *AMA Arch Ind Health* 12(2): 140-6. (Support not reported. Author affiliated with Saranac Laboratory, NY.)

224. Schultz PN, Warren G, Kosso C, Rogers S. 1982. Mutagenicity of a series of hexacoordinate cobalt(III) compounds. *Mutat Res* 102(4): 393-400. (Supported by NIH and the Agricultural Experiment Station, Montana State University. Authors affiliated with Montana State University, MT.)

225. Schwarz Y, Kivity S, Fischbein A, Abraham JL, Fireman E, Moshe S, Dannon Y, Topilsky M, Greif J. 1998. Evaluation of workers exposed to dust containing hard metals and aluminum oxide. *Am J Ind Med* 34(2): 177-182. (Support not reported. Authors affiliated with Tel Aviv Sourasky Medical Center, Israel; Bar Ilan University, Israel; State University of New York Health Science Center, NY; Health Insurance Institution of the General Federation of Labour in Eretz, Israel.)

226. Seiler RL. 2006. Comment on "Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: Possible implications for the childhood leukemia cluster", by P.R. Sheppard, G. Ridenour, R.J. Speakman, and M.L. Witten. *Appl Geochem* 21: 713-714. (Support not reported. Author affiliated with the U.S. Geological Survey.)

227. Sesana G, Cortona G, Baj A, Quaianni T, Colombo E. 1994. Cobalt exposure in wet grinding of hard metal tools for wood manufacture. *Sci Total Environ* 150(1-3): 117-119. (Support not reported. Authors affilitated with Desio Hospital, Italy; Local Health Unit #63, Italy.)

228. Sheppard PR, Ridenour G, Speakman RJ, Witten ML. 2006a. Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: possible implications for the childhood leukemia cluster. *Appl Geochem* 21: 152-165. (Supported by the Gerber Foundation and the Cancer Research and Prevention Foundation. Authors affiliated with University of Arizona, AZ; University of Missouri, MO.)

229. Sheppard PR, Speakman RJ, Ridenour G, Witten ML. 2006b. Reply to comment on "Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: Possible implications for the childhood leukemia cluster" by R. Seiler. *Appl Geochem* 21: 715-723. (Support not reported. Authors affiliated with University of Arizona, AZ; University of Missouri, MO.)

230. Sheppard PR, Speakman RJ, Ridenour G, Witten ML. 2006c. Reply to comment on "Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: Possible implications for the childhood leukemia cluster", by Blasland, Bouck & Lee, Inc. *Appl Geochem* 21: 1083-1088. (Support not reported. Authors affiliated with University of Arizona, AZ; University of Missouri, MO.)

231. Sheppard PR, Speakman RJ, Ridenour G, Witten ML. 2007a. Temporal variability of tungsten and cobalt in Fallon, Nevada. *Environ Health Perspect* 115(5): 715-9. (Supported by the Gerber Foundation, the Cancer Research and Prevention Foundation and the U.S. EPA. Authors affiliated with University of Arizona, AZ; Smithsonian Institution, MD; Internal Medicine, NV.)

232. Sheppard PR, Toepfer P, Schumacher E, Rhodes K, Ridenour G, Witten ML. 2007b. Morphological and chemical characteristics of airborne tungsten particles of Fallon, Nevada. *Microscopy and Microanalysis* 13(4): 296-303. (Supported by the Gerber Foundation and the Cancer Research and Prevention Foundation. Authors affiliated with University of Arizona, AZ; McCrone Associates, Inc, IL.)

233. Sheppard PR, Speakman RJ, Ridenour G, Glascock MD, Farris C, Witten ML. 2007c. Spatial patterns of tungsten and cobalt in surface dust of Fallon, Nevada. *Environ Geochem Health* 29(5): 405-12. (Supported by the Gerber Foundation and the Cancer Research and Prevention Foundation. Authors affiliated with University of Arizona, AZ; Smithsonian Institution, MD; University of Missouri, MO.)

234. Sheppard PR, Speakman RJ, Ridenour G, Witten ML. 2007d. Using lichen chemistry to assess airborne tungsten and cobalt in Fallon, Nevada. *Environ Monit Assess* (Epub): 8 pp. (Supported by the Gerber Foundation and the Cancer Research and Prevention Foundation. Authors affiliated with University of Arizona, AZ; University of Missouri, MO.)

235. Sheppard PR, Speakman RJ, Ridenour G, Witten ML. Response to: Tungsten and cobalt in Fallon, Nevada: association with childhood leukemia (2008). *Environ Health Perspect* 116(5): A197. (Support not reported. Authors affiliated with University of Arizona, AZ; University of Missouri, MO.)

236. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Morimoto K. 1988. The existence of specific antibodies to cobalt in hard metal asthma. *Clin Allergy* 18(5): 451-60. (Support not reported. Authors affiliated with Osaka University, Japan; Takatsuki Red Cross Hospital, Japan.)

237. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Kato M, Heki S, Morimoto K. 1989. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. *Chest* 95(1): 29-37. (Support not reported. Authors affiliated with Osaka University, Japan; Takatsuki Red Cross Hospital, Japan.)

238. Simcox NJ, Stebbins A, Guffey S, Atallah R, Hibbard R, Camp J. 2000. Hard metal exposures. Part 2: Prospective exposure assessment. *Appl Occup Environ Hyg*

15(4): 342-353. (Support not reported. Authors affiliated with University of Washington, WA; Department of Labor and Industries, WA.)

239. Singh I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in Saccharomyces cerevisiae. *Mutat Res* 117(1-2): 149-52. (Support not reported. Author affiliated with Haryana Agricultural University, India.)

240. Sjogren I, Hillerdal G, Andersson A, Zetterstrom O. 1980. Hard metal lung disease: Importance of cobalt in coolants. *Thorax* 35(9): 653-659. (Support not reported. Authors affiliated with Sanvikens Jernverk, Sweden; University Hospital, Sweden.)

241. Sprince NL, Chamberlin RI, Hales CA, Weber AL, Kazemi H. 1984. Respiratory disease in tungsten carbide production workers. *Chest* 86(4): 549-57. (Support not reported. Authors affiliated with Harvard Medical School, MA; Massachusetts Institute of Technology, MA; Massachusetts Eye and Ear Infirmary, MA.)

242. Sprince NL, Oliver LC, Eisen EA, Greene RE, Chamberlin RI. 1988. Cobalt exposure and lung disease in tungsten carbide production. A cross-sectional study of current workers. *Am Rev Respir Dis* 138(5): 1220-6. (Support not reported. Authors affiliated with Harvard Medical School, MA; Massachusetts Institute of Technology, MA.)

243. Stebbins AI, Horstman SF, Daniell WE, Atallah R. 1992. Cobalt exposure in a carbide tip grinding process. *Am Ind Hyg Assoc J* 53(3): 186-192. (Support not reported. Authors affiliated with University of Washington, WA; University of Kentucky, KY.)

244. 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(6): 793-803. (Supported by R. Scripsick at LANL. Authors affiliated with NIOSH; Los Alamos National Laboratory, NM.)

245. Steinberg KK, Relling MV, Gallagher ML, Greene CN, Rubin CS, French D, Holmes AK, Carroll WL, Koontz DA, Sampson EJ, Satten GA. 2007. Genetic studies of a cluster of acute lymphoblastic leukemia cases in Churchill County, Nevada. *Environ Health Perspect* 115(1): 158-64. (Supported by the National Cancer Institute, National Institutes of Health, the State of Tennessee and the American Lebanese Syrian Associated Charities. Authors affiliated with CDC; St. Jude Children's Research Hospital, TN; New York University School of Medicine, NY.)

246. Steinbrech DS, Mehrara BJ, Saadeh PB, Greenwald JA, Spector JA, Gittes GK, Longaker MT. 2000. VEGF expression in an osteoblast-like cell line is regulated by a hypoxia response mechanism. *Am J Physiol Cell Physiol* 278(4): C853-C860. (Support not reported. Authors affiliated with New York University Medical Center, NY.)

247. Steinmaus C, Lu M, Todd RL, Smith AH. 2004. Probability estimates for the unique childhood leukemia cluster in Fallon, Nevada, and risks near other U.S. Military aviation facilities. *Environ Health Perspect* 112(6): 766-771. (Supported by NIEHS and the University of California Center for Occupational and Environmental Health. Authors affiliated with University of California - Berkeley, CA; University of California - San Francisco, CA; Nevada State Health Division, NV.)

248. Stettler LE, Groth DH, Platek SF. 1983. Automated characterization of particles extracted from human lungs: three cases of tungsten carbide exposure. *Scan Electron Microsc* (Pt 1): 439-448. (Support not reported. Authors affiliated with NIOSH.)

249. Stopford W, Turner J, Cappellini D, Brock T. 2003. Bioaccessibility testing of cobalt compounds. *J Environ Monit* 5(4): 675-80. (Supported by the Cobalt Development Institute, UK. Authors affiliated with Duke University, NC; Angeline Kirby Memorial Health Center, PA.)

250. Sueker JK. 2006. Comment on "Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: Possible implications for the childhood leukemia cluster" by P.R. Sheppard, G. Ridenour, R.J. Speakman, and M.L. Witten. *Appl Geochem* 21: 1083-1085. (Support not reported. Author affiliated with Blasland, Bouk and Lee, Inc., CO.)

251. Sunderman FW, Jr. 1989. Carcinogenicity of metal alloys in orthopedic prostheses: clinical and experimental studies. *Fundam Appl Toxicol* 13(2): 205-216. (Support not reported. Author affiliated with University of Connecticut Medical School, CT.)

252. Swierenga SH, Gilman JP, McLean JR. 1987. Cancer risk from inorganics. *Cancer Metastasis Rev* 6(2): 113-154. (Support not reported. Authors affiliated with Bureau of Drug Research, Health and Welfare, Canada; University of Guelph, Canada; Bureau of Radiation and Medical Devices Health and Welfare, Canada.)

253. Teschke K, Marion SA, van Zuylen MJA, Kennedy SM. 1995. Maintenance of stellite and tungsten carbide saw tips: Determinants of exposure to cobalt and chromium. *Am Ind Hyg Assoc J* 56: 661-669. (Supported by the Workers Compensation Board of British Columbia. Authors affiliated with University of British Columbia, Canada; Wageningen Agricultural University, Netherlands.)

254. ThomasNet. 2008. *Metals: Carbide*. Thomas Publishing. http://www.thomasregisterdirectory.com. Accessed: 9/24/08.

255. 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. (Support not reported. Authors affiliated with Universitat de Barcelona, Spain; Dr. Echevarne Laboratoires, Spain.)

256. Tozawa T, Kitamura H, Koshi K, Ikemi Y, Ambe K, Kitamura H. 1981. [Experimental pneumoconiosis induced by cemented tungsten and sequential concentrations of cobalt and tungsten in the lungs of the rat (author's translation)]. *Sangyo Igaku* 23(3): 216-226. As cited in IARC 2006. (Support unknown due to foreign language. Authors affiliated with Yokohama City University of Medicine, Japan; National Institute of Industrial Health, Japan.)

257. Tso WW, Fung WP. 1981. Mutagenicity of metallic cations. *Toxicol Lett* 8(4-5): 195-200. (Support not reported. Authors affiliated with the Chinese University of Hong Kong, China.)

258. Tüchsen F, Jensen MV, Villadsen E, Lynge E. 1996. Incidence of lung cancer among cobalt-exposed women. *Scand J Work Environ Health* 22(6): 444-450. (Supported by the Danish Working Environment Fund and the Danish Health Fund. Authors affiliated with National Institute of Occupational Health, Denmark; Danish Cancer Society, Denmark.)

259. Tucker Jr. RC. 1996. Chapter 11: Advanced Thermal Spray Deposition Techniques. In *Handbook of Deposition Technologies for Films and Coatings. Science, Technology and Applications*. Buntash R, ed. Park Ridge, NJ: Noyes Publications. (Support not reported. Author affiliation not indicated. Editors affiliated with University of California, CA.)

260. Upadhyaya GS. 1998. Classification and Applications of Cemented Carbides. In *Cemented Tungsten Carbides. Production, Properties, and Testing*. Westwood, NJ: Noyes Publications. 403 pp. (Support not reported. Authors affiliated with Indian Institute of Technology, India.)

261. USDC. 2005. *Sawmills: 2002 Economic Census. Manufacturing - Industry Series*. EC02-311-321113. U.S. Census Bureau, U.S. Department of Commerce.

262. USGS. 2004. *Mineral Industry Surveys: Tungsten in 2003*. U.S. Department of Interior, U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/tungsten/.

263. USGS. 2005. *Tungsten Recycling in the United States in 2000*. Open-File Report 2005-1028. U.S. Department of the Interior, U.S. Geological Survey. 26 pp.

264. USGS. 2008a. *Mineral Industry Surveys: Cobalt in October, November and December 2007*. Reston, VA: U.S. Department of the Interior, U.S. Geological Survey. 12 pp. http://minerals.usgs.gov/minerals.

265. USGS. 2008b. *Mineral Industry Surveys: Tungsten in January 2008*. Reston, VA: U.S. Department of the Interior, U.S. Geological Survey. 6 pp. http://minerals.usgs.gov/minerals.

266. 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. (Supported by the Belgian Federal Office for Scientific, Technical and Cultural Affairs. Authors affiliated with Free University Brussels, Belgium; Catholic University of Louvain, Belgium.)

267. Wei HJ, Luo XM, Yang SP. 1985. Effects of molybdenum and tungsten on mammary carcinogenesis in SD rats. *J Natl Cancer Inst* 74(2): 469-473. (Supported by Climax Molybdenum Co. and Texas Tech University. Authors affiliated with Chinese Academy of Medical Sciences, China; Texas Tech University, TX.)

268. Wennig R, Kirsch N. 1988. Tungsten. In *Handbook on Toxicity of Inorganic Compounds*. Seiler HG, Sigel H, Sigel A, eds. New York: Marcel Dekker, Inc. p. 731-738. (Support not reported. Authors affiliated with Laboratoire National de Santé, Luxembourg; Umweltamt, Luxembourg.)

269. White MA, Dyne D. 1994. Biological monitoring of occupational cobalt exposure in the United Kingdom. *Sci Total Environ* 150(1-3): 209-13. (Support not reported. Authors affiliated with Occupational Medicine and Hygiene Laboratory, UK.)

270. 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. (Support not reported. Authors affiliated with INRS, France; Institut Universitaire de Médecine du Travail et de l'Environnement de Grenoble.)

271. Wong PK. 1988. Mutagenicity of heavy metals. *Bull Environ Contam Toxicol* 40(4): 597-603. (Supported by Ho Yin and Ho Tim Research Grant and the Chinese University of Hong Kong. Author affiliated with Chinese University of Hong Kong.)

272. WSDLI. 1995. *Hard-Metal Workers Face Risks of Cobalt, Cadmium*. State of Washington Department of Labor and Industries. http://www.lni.wa.gov/Safety/Basics/HazAlerts/951a.asp. Last accessed: 1/24/05.

273. Yamada Y, Kido T, Honda R, Ishizaki M, Tsuritani I, Yamaya H, Nogawa K. 1987. Analysis of dusts and evaluation of dust exposure in a hard metal factory. *Ind Health* 25(1): 1-10. (Support not reported. Authors affiliated with Kanazawa Medical University, Japan.)

274. 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. (Supported by the Commission of the European Communities. Authors affiliated with Università di Torino, Italy.)

275. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen* 19 Suppl 21: 2-141. (Support not reported. Authors affiliated with NIEHS; Microbiological Associates, Inc., MD; SRI International, CA.)

# Glossary of Terms

**Alveolitis:** inflammation of an alveolus.

**Aneugenic:** Affecting cell division and the mitotic spindle apparatus, resulting in loss or gain of whole chromosomes and thereby inducing aneuploidy.

**Boiling point:** The boiling point of the anhydrous substance at atmospheric pressure (101.3 kPa) unless a different pressure is stated. If the substance decomposes below or at the boiling point, this is noted (dec). The temperature is rounded off to the nearest °C.

**Bronchoalveolar lavage:** A technique used to obtain a sample of the cells, fluids, and other materials present in the very small airways and alveoli of the lung by instilling saline into the airway via a bronchoscope.

**Delphi method:** A systematic interactive forecasting method based on independent inputs from selected experts.

**Density:** The density for solids and liquids is expressed in grams per cubic centimeter ($g/cm^3$) and is generally assumed to refer to temperatures near room temperature unless otherwise stated. Values for gases are generally the calculated ideal gas densities in grams per liter at 25°C and 101.325 kPa.

**Exogenous:** Due to an external cause; not arising within the organism.

**Fenton reaction:** The iron(II)-salt–dependent decomposition of hydrogen peroxide generating a highly reactive hydroxyl radical.

**Formamido-pyrimidine DNA glycosylase (Fpg):** An enzyme that functions in DNA base-excision repair by recognizing and removing oxidized DNA bases, including apurinic sites, formamido-pyrimidine moieties (FAPY lesions), and 8-oxo-deoxyguanosine, resulting in a single nucleotide gap in the DNA.

**Goodpasture's syndrome:** An autoimmune disorder that affects the lungs and kidneys. It is rapidly progressive and usually fatal.

**Hardness:** The degree to which a substance will resist cutting, abrasion, penetration, bending, and stretching. An indicated hardness may differ depending on the apparatus or method measuring the hardness. (See also Mohs hardness and Vickers hardness, below)

**Henry's Law constant at 25°C:** The ratio of the aqueous-phase concentration of a chemical to its equilibrium partial pressure in the gas phase. The larger the Henry's law constant the less soluble it is (greater tendency for vapor phase).

**Hot isostatic pressing:** A process of reheating in high-pressure ovens under argon at 14,000 to 22,000 psi at temperatures slightly below the sintering temperature (see Isostatic pressing).

**Hydrostatic pressing:** Compaction on a hydraulic or hydrostatic press.

**Isostatic pressing:** Compaction by pressure exerted uniformly in all directions on a preformed flexible mold in a pressure vessel.

**ICD-(8 or 9):** The International Classification of Diseases ($8^{th}$ or $9^{th}$ edition). Published by World Health Organization, ICD codes are specific three-character codes used to describe a patient's health care condition.

**International Organization for Standardization (ISO):** A non-governmental organization made up of representatives from national standards bodies that serves as an international standard-setting body. The organization is usually referred to as "ISO," which is a short form of the name chosen by the founders of the organization rather than a true acronym.

**Log octanol-water partition coefficient (log $K_{ow}$):** The ratio of concentrations of a substance in octanol and in water, when dissolved in a mixture of octanol and water.

**Mass median aerodynamic diameter (MMAD):** The geometric mean aerodynamic diameter. Fifty per cent of the particles by weight will be smaller that the MMAD, 50% will be larger.

**Melting point:** The melting point of the substance at atmospheric pressure (101.3 kPa). When there is a significant difference between the melting point and the freezing point, a range is given. In case of hydrated substances (i.e., those with crystal water), the apparent melting point is given. If the substance decomposes at or below its melting point, this is noted (dec). The temperature is rounded off to the nearest °C.

**Mohs hardness (test):** A measure of the resistance of a smooth surface to scratching or abrasion, expressed in terms of a scale. The Mohs scale is composed of 10 minerals that have been given arbitrary hardness values ranging from 1 (talc) to 10 (diamond). The Mohs hardness of a mineral will fall between the highest numbered mineral that will not scratch the substance and the lowest numbered mineral on the scale that will scratch the substance.

**Molecular weight:** The molecular weight of a substance is the weight in atomic mass units of all the atoms in a given formula. The value is rounded to the nearest tenth.

**MTT assay:** An assay for cell viability and growth based on metabolic reduction of the yellow tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide or MTT) to form insoluble purple formazan crystals, a reaction that is dependent on the presence of functional mitochondria in viable cells. The detergent-solubilized formazan crystals are quantified spectrophotometrically.

**Neoplasm:** An abnormal mass (or group) of cells.

**Physical state:** Substances may either be gases, liquids, or solids according to their melting and boiling points. Solids may be described variously as amorphous, powders,

pellets, flakes, lumps, or crystalline; and the shape of the crystals is specified if available. Solids also may be described as hygroscopic or deliquescent depending upon their affinity for water.

**Powder metallurgy:** A process for forming and fabricating parts from metal powder that is compacted in a mold under pressure, then sintered in an oven at high temperatures that cause the powder to coalesce into a solid.

**Respirable fraction:** That portion of dust that can reach the lower, or gas exchange, part of the respiratory system.

**Screening:** A process for separating grains of various sizes into two or more size-range portions by means of porous or woven-mesh screening media.

**Sintering:** Forming a coherent bonded mass by heating metal powders without melting.

**Spray drying:** A process involving the atomization of a liquid feedstock into a spray of droplets and exposing the droplets to hot air in a drying chamber to evaporate the moisture from the droplets.

**Stellite:** A cobalt-based alloy with chromium and other metals used to make cutting tools and for surfaces subject to heavy wear.

**Toughness:** The ability of a material to withstand great strain without tearing or breaking.

**Vickers hardness (test):** A method for measuring the hardness of metals, particularly those with extremely hard surfaces. In the Vickers hardness test, the surface is subjected to a standard pressure for a standard length of time by a pyramid-shaped diamond. The diagonal of the resulting indentation is measured under a microscope and the Vickers hardness value is determined from a conversion table.

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# Appendix A. Fallon, Nevada leukemia cluster

Studies on the leukemia cluster (Section A.1) and on exposure to cobalt and tungsten (Section A.2) in Fallon, NV are discussed below.

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## A.1 Description of cluster

A unique cluster of childhood leukemia, characterized by a steep increase in the number of cases, short time frame in which the cases were diagnosed, and small population of the source area, was identified in the city of Fallon in Churchill County, Nevada (population = 23,982). The cluster (as defined by Steinmaus *et al*. [2004]), consisted of 11 biopsy-confirmed cases (10 with acute lymphocytic leukemia [ALL] and 1 acute myelocytic leukemia [AML]) that were identified among children residing in Churchill County from 1999 to 2001; 5 additional cases were identified from 1997 to 2002 among children who were no longer residents at the time of diagnosis but who had lived in Churchill County prior to diagnosis. Steinmaus *et al*. reported that the age-standardized rate ratio (RR) for childhood leukemia was 12.0 (95% confidence interval [CI] = 6.0 to 21.4, $P = 4.3 \times 10^{-9}$; 11 observed cases). Because risk estimates and associated statistical testing of clusters are subject to bias, they also calculated an incidence of 11.2 (95% CI = 3.6 to 26.3) for 5 cases diagnosed after the investigation began in July 2000. The authors concluded that a cluster of this magnitude would be expected to occur in the United States by chance once about every 22,000 years and, thus, was unlikely to have occurred by chance. An additional case was identified in December 2004 (Sheppard *et al.* 2007a). To date, the cause of the leukemia cluster has not been identified. Some potential causes that have been either evaluated or proposed are (1) proximity to a military aviation base, (2) population admixing, and (3) environmental exposure to toxins or biological agents from natural or anthropogenic sources. A cross-sectional study was conducted to evaluate the third possibility as discussed below.

In 2001, the Centers for Disease Control (CDC) conducted a cross-sectional, case-comparison investigation that included 14 children who resided in Churchill County before diagnosis of leukemia. Each case was matched on sex and age to approximately 4 comparison children (Rubin *et al.* 2007). Case families (parents, siblings, and adult care-takers living in the house) and parents of the comparison children were also enrolled in the study. A total of 14 case families and 55 comparison families were enrolled in the study. Questionnaire data, biological samples, and environmental samples (indoor air, play yard soil, household dust, and tap water) were collected from the study participants or their homes. Biological and environmental samples were measured for heavy metals, pesticides, polychlorinated biphenyls, and volatile organic compounds (VOCs). In addition, biological samples were tested for viral infections, and environmental samples were tested for radon and radionuclides. Questionnaire data were used to assess lifestyle and demographic factors associated with leukemia. Laboratory results were compared with either levels associated with health effects or the geometric mean and 95$^{th}$ percentile levels from the *Second National Report on Human Exposure to Environmental Chemicals*, which is based on population data collected as part of the National Health and Nutrition Examination Survey (NHANES). The results related to tungsten exposure are discussed in detail below.

Levels of tungsten in environmental samples were compared with published standards for that element. Biological sampling revealed community-wide exposure to tungsten with almost 80% of the participants having urinary tungsten levels above the NHANES 90$^{th}$ percentile, and the median tungsten levels were almost 10-fold higher than the 1999 NHANES median level for tungsten. Elevated levels of tungsten were found in the tap

water relative to national comparison values. [Currently there is no reference level for tungsten in water.] High levels of urinary tungsten also were found among residents of another Nevada community (Yerington), and elevated levels were found in tap water; [urinary levels of children from Churchill County were approximately 2 times higher than among children in Yerington, but the levels in the total population (adults and children) were similar]. Urinary levels of tungsten did not differ between case and comparison children or case and comparison families. The authors concluded that the small number of cases and length of time between diagnosis and exposure assessment limited their ability to find an association between leukemia and environmental exposure.

Significantly elevated ORs in the case-control analyses were found for exposure to ethylbenzene (case children vs. control children), and for older parental age of the father at the time of the child's birth. No significant associations were found for exposure to other VOCs or pesticides or for other lifestyle and demographic factors (including exposure to ionizing radiation). The authors concluded that the small number of cases and length of time between diagnosis and exposure assessment limited their ability to find an association between leukemia and environmental exposure. In a genetic susceptibility study of 11 of the 15 children with childhood leukemia and 42 age- and sex-matched community controls, a possible association was found between sulfate oxidase (SUOX 1) (which is inhibited by tungsten) gene alleles and case or control status (Steinberg *et al.* 2007).

## A.2 Studies on exposure to cobalt and tungsten

As described in Section 2 and in more detail below, a hard-metal manufacturing plant is located in Fallon, NV. ATSDR (2003) conducted an air exposure pathway assessment of this facility. Outdoor ambient air levels were based on historical data from the Nevada Bureau of Air Quality, which included data from 2 monitoring stations operating at different times from 1972 to 1998, meteorological observations, and recent (2002) sampling (2 locations); however, the samples were not analyzed for tungsten. They also reviewed U.S. Environmental Protection Agency databases for information on air emissions. ATSDR conducted air-modeling analysis of historical emissions data (pre-1994 emissions) and did not find a spatial relationship between predicted exposure levels for particulate matter and the location of leukemia cases. [Particulate matter emission content was not reported, but was assumed to consist of several metals such as antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and tungsten.]

No epidemiological studies were found that evaluated the relationship between exposure to cobalt–tungsten carbide hard metals and childhood leukemia.

### *A.2.1 Studies by Sheppard and colleagues and authors' responses to comments*

A series of related studies by Sheppard and colleagues (Sheppard *et al.* 2006a; Sheppard *et al*. 2007a,c,d) have reported elevated airborne tungsten and cobalt levels in the vicinity of a hard-metal manufacturing facility in Fallon, NV. The first study (Sheppard *et al*. 2006a) measured trace-metal concentrations, including tungsten and cobalt, in airborne particulates collected at two different times of the year (March–April and November of 2004) in Fallon and four nearby towns for comparison purposes using 10 portable, high-

volume particulate air samplers (5 in Fallon and 5 in surrounding towns) (Sheppard *et al.* 2006a,b,c). Of nineteen elements measured, only tungsten and cobalt air concentrations were consistently higher in Fallon than in the surrounding towns; median air levels for tungsten and cobalt were significantly ($P$ = 0.001 to 0.002) higher in Fallon than in the four comparison towns as a group.

Across the spring and fall sampling periods combined, median air concentrations for tungsten ranged from 0.1 to 40.9 ng/m$^3$ in Fallon, and from 0.02 to 0.16 ng/m$^3$ in the comparison towns. For cobalt, median air concentrations ranged from 0.04 to 7.5 ng/m$^3$ in Fallon, and from 0.04 to 0.58 ng/m$^3$ in the comparison towns. Sheppard *et al*. (2006b) noted that even when the data were presented in mass/mass units, the levels were higher in Fallon. Sheppard *et al*. (2006b) also noted that many other elements were measured besides tungsten and cobalt, but none of them showed consistent differences or patterns between Fallon and the comparison towns; and, as such they served the function of a conservative trace element for the analysis. Further, Sheppard *et al*. (2006c) explained why the seasonal data was analyzed individually. They noted that during their assessment, the March collection period was windy, warm, and dry, but the November collection period was relatively calm, cool, and wet. They noted that such a large difference in weather rendered inter-seasonal comparisons of absolute values of airborne particulates of little value. They noted that in both seasons, Fallon had significantly higher levels of airborne tungsten and cobalt relative to comparison towns, airborne tungsten and cobalt co-varied at the daily or sub-weekly scale, and wind speed correlated to at least some degree with airborne tungsten levels. They concluded that replication of these patterns across two different seasons provided stronger evidence for elevated tungsten and cobalt being a distinctive environmental feature of Fallon than if these relative patterns had been demonstrated for just one season.

Although tungsten is naturally present in the soils and rocks in the area (ATSDR 2003) the authors suggested that the source of cobalt and tungsten was not from a natural deposit because tungsten levels were not elevated in any comparison town, tungsten and cobalt particles varied temporally and spatially (indicating a single source), cobalt is not naturally abundant in the area, and high winds decreased tungsten loading in Fallon. [The opposite effect for tungsten loading and high winds would be expected if the source were natural.] The authors investigated whether the hard-metal facility in Fallon could be the source of the elevated tungsten and cobalt levels in the air. They reported (1) that loading of both tungsten and cobalt dropped off steeply 3 km from the hard-metal facility in Fallon and then slowly beyond 3 km, and (2) that the temporal variability of tungsten and cobalt loading also dropped off with distance from the hard-metal facility.

In a follow-up study (Sheppard *et al.* 2007b), airborne dust particles were isolated and analyzed with automated electron microprobe and wavelength-dispersive spectrometry revealing that the tungsten particles were generally combined with cobalt and other elements such as chromium, iron, and copper, and the authors concluded that the particles were most consistent with identification as tungsten carbide. Based on the results of this analysis, the authors concluded that the airborne tungsten in Fallon is anthropogenic in origin.

To increase the spatial resolution of tungsten and cobalt levels in Fallon, Sheppard *et al.* (2007c) collected surface dust in a grid pattern within and outside of Fallon and analyzed for 20 elements, including tungsten and cobalt. They noted that surface dust is an ideal indicator of atmospheric deposition for heavy metals and that their methodology of collecting samples in a grid would allow them to map differing concentrations of atmospheric deposition of heavy metals and thereby pinpoint the sources of unusual airborne metals. In total, 125 surface dust samples were collected within Fallon and outside of Fallon to establish background concentrations. Within Fallon, the grid cell length was 0.5 km and outside of Fallon the grid cell length was extended to 2 to 5 km to maximize the spatial extent of monitoring. Sampling took place after a three-week period without substantial rain, and samples were taken mostly from paved surfaces. The authors noted that there was little spatial variability among the measured elements except for tungsten, which had a coefficient of variability of 732%. The next highest coefficient of variability was cobalt at 77%, followed by arsenic at 71%. The peak levels for tungsten (934 ppm) and cobalt (98 ppm) overlapped exactly spatially, with the same sampling location having the highest value for both. The authors reported that based on the other sampling points, background levels were less than 10 ppm for tungsten and less than 15 ppm for cobalt. They noted that based on the results of their analysis, the source of the airborne metals could be pinpointed to the vicinity of the hard-metal production facility located within Fallon.

Sheppard *et al.* (2007d) also performed an analysis on lichens to compare airborne levels of tungsten and cobalt in Fallon (N = 10) with levels at outcrops located north, east, south, and west of Fallon (N = 20) and at least 20 km away from the town center. They reported higher concentrations of tungsten (12.5 times higher, $P < 0.001$) and cobalt (2.0 times higher, $P = 0.06$) in lichens from Fallon compared with the lichens outside of Fallon. [The authors noted that lichens integrate their environment throughout their entire life and can reflect atmospheric chemistry and deposition of elements across decades.] There were no differences in the concentrations of tungsten or cobalt across rock samples.

Dendrochemistry (the study of element concentrations in tree rings) was used by Sheppard *et al.* (2007a) to assess the temporal variability of tungsten and cobalt in Fallon (N = 5) and three surrounding towns (N = 6). To test the accuracy of dendrochemistry for tungsten, a separate analysis (validation study) using cottonwood trees and Douglas-firs or cottonwood trees only was performed in a small town in Oregon with a known industrial source of airborne tungsten. This study demonstrated stable levels before the onset of the tungsten industry with levels increasing thereafter. The study on Fallon and comparison towns used cottonwood trees. For Fallon, the authors reported that for the time period from 1989 to 1992, before the onset of the leukemia cases, median tree-ring tungsten levels were not statistically significantly different from the comparison towns; however, thereafter, levels in Fallon increased, whereas levels in comparison towns remained relatively constant. The authors noted that cobalt levels in Fallon tree rings were consistently higher than in comparison towns, but there was no significant increase across time within Fallon. In a separate publication, Sheppard *et al.* (2008) acknowledged that during the time period that centered on 1991, there were no statistical differences between Fallon and surrounding towns. However, during the time period that centered on

1995 [the period just before the onset of the cluster], Fallon tree-ring tungsten levels started trending upward and were statistically significantly higher than levels seen in the comparison towns. During the following time periods, the tungsten levels in Fallon continued trending upward and remained higher than comparison towns with significance levels at or near $P = 0.05$.

Sheppard *et al*. (2008) concluded that multiple environmental indicators have been used (levels in air samples, surface dust samples, lichens, and tree rings) that incorporate environmental conditions differently from one another, and yet they have all shown elevated levels of tungsten in air when compared with surrounding towns. Further, they concluded that tungsten particulates in Fallon are anthropogenic in origin. However, they did not consider that their studies had demonstrated that exposure to tungsten caused leukemia, and they pointed out the need for direct biomedical testing to establish the cause of the leukemia cases.

### *A.2.2 Published commentaries on the Sheppard* et al. *findings*

Seiler (2006) suggested that the comparisons between towns was made based on tungsten and cobalt loadings without evaluating concentrations or normalizing the loadings to a conservative trace element; therefore, it was impossible to tell if the dust had higher levels of tungsten and cobalt, or if Fallon was simply a dustier town. Sueker (2006) also commented that the data, as presented in Sheppard *et al.* (2006a) did not allow for the determination of whether tungsten and cobalt were more abundant in the dust or if Fallon were simply dustier. Seiler noted that the data presented by Sheppard did not confirm the presence of tungsten carbide but only of tungsten in the particulate matter. Seiler also suggested that Sheppard *et al.* did not account for the possibility of higher tungsten levels in the dust simply due to its unique geohydrologic history.

Sueker (2006) expressed concerns about the way wind speed and direction were used in the Sheppard assessment. Sueker noted that Sheppard *et al.* developed two regressions for the two seasonal sampling periods, and that if these data were pooled, the relationship between wind speed and loadings disappeared. Similarly, Sueker noted that if outliers that Sheppard omitted from the analysis [without satisfactory explanation] were included, the relationship disappeared.

Sueker (2006) made note of the report by Sheppard that tungsten loadings dropped off rapidly to typical ambient loadings within 2 km of the hard-metal facility. She pointed out, however, that many of the homes of the leukemia cases fall outside of the modeled impacted area and cited the ATSDR 2003 study on air exposure pathway assessment of this facility discussed above.

Schell and Pardus (2008) commented on the Sheppard *et al*. dendrochemistry study and suggested that the data do not support the conclusions drawn; but rather, if the data support anything, it is that the environmental tungsten levels and leukemia cases are not causally related. Based on an evaluation of graphic representations of the data presented in Sheppard *et al*. (2007a) (they noted that the data were not provided) the authors suggested that the increase in tungsten levels in the trees actually occurred during the 2001 to 2004 time period, which is well after the onset of the childhood leukemia cluster.

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# Appendix B. Exposure data for hard-metal manufacture: Steps 2 and 3

The studies reporting process-specific air concentrations and biological levels for cobalt and tungsten for Steps 2 and 3 of hard-metal manufacture were briefly summarized in Tables 2-3 and 2-4. The same studies are described in more detail below in Tables B-1 and B-2.

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**Table B-1. Hard-metal exposure levels from manufacturing operations (Step 2) (levels are for cobalt unless otherwise noted)**

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m³ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Scrap reclamation | | NA | *Cobalt respirable mass %* | Stefaniak *et al*. 2007 |
| scrap loader | 192 {1} | | 9 | (U.S., NR) |
| large crusher | 64 {1} | | 12 | |
| small crusher | 21 {1} | | 12 | |
| ball mill | 132 {1} | | 7 | |
| Powder mixing | 145 {1} | | 14 | |
| Powder mixing | 70 {1} | | 21 | |
| Spray drying | 9 {1} | | 13 | |
| Screening | 81 {1} | | 15 | |
| Pressing | 13 {1} | | 14 | |
| **Cobalt** | | | "P" = personal sampling | Kraus *et al*. 2001 |
| Production of WC | P: 0.39 {1} | 2.1 (0.31–5.7)[b] {4} | "S = stationary sampling | (Germany, NR) |
| Powder processing | P: NR (7.9–64.3) {4} | 28.5 (0.75–227.8)[b] {14} | Only the range was presented for air monitoring data, single values reflect samples of N = 1 | |
| Forming | P: NR (0.61–2.82) {5} | 13.5 (0.75–106.4)[b] {23} | | |
| ″ | S: 1.32 {1} | NA | | |
| Pressing | P: NR (0.87–116.0) {3} | 5.5 (0.36–35.9)[b] {30} | | |
| Sintering | P: 343.0 {1} | 4.1 (0.31–9.6)[b] {6} | | |
| ″ | S: 1.3 {1} | NA | | |
| Heavy alloy prod. | P: NR (0.85–1.84) {2} | 1.6 (1.1–2.2)[b] {3} | | |
| ″ | S: NR (0.63–8.50) {3} | NA | | |
| Maintenance | NA | 3.0 (1.3–4.7)[b] {2} | | |
| **Tungsten** | | | | |
| Production of WC | P: 19.1 {1} | 42.1 (10.0–60.6)[b] {4} | | |
| Powder processing | P: NR (177.0–254.0) {4} | 12.2 (2.6–25.1)[b] {14} | | |
| Forming | P: NR (7.8–97.4) {5} | 10.7 (0.33–33.1)[b] {23} | | |
| ″ | S: 6.2 {1} | NA | | |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m³ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Pressing<br>Sintering<br>″<br>Heavy alloy prod.<br><br>Maintenance | P: NR (5.3–211.0) {3}<br>P: 12.1 {1}<br>S: 5.9 {1}<br>P: NR (125.0–417.0) {2}<br>S: NR (50.0–163.0) {3}<br>NA | 8.6 (1.5–71.0)[b] {30}<br>12.5 (2.1–46.8)[b] {6}<br>NA<br>24.9 (2.6–50.5)[b] {3}<br>NA<br>3.4 (1.5–5.3)[b] {2} | | |
| Powder preparation<br>rotation<br>full-time<br>Press<br>rubber<br>steel<br>Shaping<br>Sintering | <br>459 (7–6,390) {60}<br>147 (26–378) {12}<br><br>339 (48–2,910) {26}<br>47 (6–248) {34}<br>97 (4–1,160) {179}<br>24 (1–145) {82} | NA | Powder preparation workers either were rotated among four different tasks on a weekly basis, or worked full-time in that area. Press machines used either rubber or steel molds, and workers were classified by mold type. | Kumagai *et al*. 1996 (Japan, NR) |
| (1) Shaping<br>(2) Sintering | (1) 141 (9–436) {9}<br>(2) 25 (7–51) {18} | *Urine*<br>(1) 1 {1}<br>(2) 2 {1}<br>*Blood (μg/dL)*<br>(1) 0.42 {1}<br>(2) 0.28 {1}<br>*Hair (ppm)*<br>(1) 25.8 {1}<br>(2) NA | Data are for two employees from a study of 4 subjects with occupational asthma<br>Exposure levels for subjects 3 and 4, who performed grinding tasks, are presented in Table B-2 | Kusaka 1996 (Japan, NR) |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m³ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Weighing (across 3 factories) | *Cobalt*<br>S: 106–478 (NR) {NR}<br>P: 418–1,600 (NR) {NR}<br>< 7 μm: 12–27 {NR}<br>*Tungsten*<br>S: 0.14–32 (NR) {NR}<br>P: 0.73–150 (NR) {NR}<br>< 7 μm: 0.023–3.1 (NR) {NR} | CoB 45.6 (1–245) {88}<br>CoU 303.6 (0.75–5,500) {88}<br>CoH 49,088 (110–910,000)[c] {90}<br>CoN 53,792 (109–580,000)[c] {92}<br>WB 1.2 (0.04–6.5) {43}<br>WU 6.7 (0.11–230) {78}<br>WH 2,147 (25–59,000)[c] {75}<br>WN 3,056 (27–105,000)[c] {82} | "S" = stationary sampling<br>"P" = personal sampling<br>< 7 μm is the concentration in the air fraction measuring less than 7 μm (considered respirable) measured by stationary sampling<br>Biological data were aggregated and summarized across workers irrespective of production stage or factory<br>Exposure levels for workers involved in grinding operations presented in Table B-2 | Sabbioni *et al.* 1994a (Bergamo Province, Italy, NR) |
| Mixing of hard-metal powders for production of diamond wheels | **Workers assessed for Co**<br>240 (19–1,360) {70}<br><br>**Subset of workers assessed for Co and W**<br>*Cobalt*<br>170 (20–350) {23}<br>*Tungsten*<br>26 (3–210) {23} | *Beginning of workweek*<br>42.6 (10.7–100.2) {70}<br>*End of workweek*<br>71.3 (16.1–210.4) {70}<br><br>**Subset of workers**<br>*cobalt*<br>61.1 (13–262) {23}<br>*tungsten*<br>2.29 (0.25–12.5) {23} | Significant correlations seen for cobalt in air and tungsten in air ($r = 0.77$, $P < 0.005$) and cobalt in urine and tungsten in urine ($r = 0.78$, $P < 0.001$).<br>Number of samples not explicitly stated, but inferred from text | Sabbioni *et al.* 1994a (Pavia, Italy, NR) |
| *Before ventilation*<br>Mixing<br>Forming<br>Pressing<br>*After ventilation*<br>Mixing<br>Forming<br>Pressing | <br>245[d] (96–967) {6}<br>772[d] (181–5,270) {10}<br>82[d] (40–541) {7}<br><br>50[d] (12–127) {9}<br>82[d] (15–190) {18}<br>29[d] (23–50) {4} | NA | Exposure levels for workers engaged in hard-metal tool sharpening operations provided in Table B-2 | Sala *et al.* 1994 (Italy, NR) |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m³ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Diamond abrasive prod<br>mold filling<br><br>sintering<br><br>mechanical working<br><br>Tool production<br><br>Hard metal alloy filling | <br>S: 220[e] (47–960) {NR}<br>P: 382[e] (76–2,600) {NR}<br>S: 102[e] (32–240) {NR}<br>P: 309[e] (238–413) {NR}<br>S: 20[e] (12–44) {NR}<br>P: 40[e] (7.1–65) {NR}<br>S: 6[e] (5–47) {NR}<br>P: 17[e] (4–28) {NR}<br>S: 2[e] (0.8–3) {NR}<br>P: 5[e] (1–107) {NR} | <br>587 (39–2,100) {NR}<br><br>193 (102–390) {NR}<br><br>67.2 (14–165) {NR}<br><br>19.4 (0.8–100) {NR}<br><br>4.8 (0.8–18) {NR} | A total of 250 air samples and greater than 600 biological samples taken for this study (data for grinders presented in Table B-2); however, number of samples not provided for specific subgroups | Mosconi *et al.* 1994 (Italy, 1991) |
| Handling of powders in hard-metal manufacture | NA | 19 (NR) {NR} | Results are from a large-scale study of occupational cobalt exposure in various industries. | White and Dyne 1994 (U.K., NR) |
| Powder preparation<br>Press<br>rubber<br>machine<br>Shaping<br>Sintering | 688 (6–6,388) {38}<br><br>473 (48–2,905) {19}<br>85 (4–407) {27}<br>126 (6–1,155) {129}<br>28 (2–145) {38} | NA | Exposure data for workers engaged in blasting, electron discharging, and wet and dry grinding provided in Table B-2 | Kusaka *et al*. 1986b (Japan, 1981–1984) |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m$^3$ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Sawing<br>Pressing/mixing<br>Sintering<br>Supervision<br>Remainder<br>Office<br><br>Sawing<br>Pressing/mixing<br>Sintering<br>Supervision<br>Remainder<br>Office | 4.3 (0.3–15) mg/m$^3$ dust {NR}<br>Cobalt content ranged from 4% to 17%: authors noted a daily load of about 3 mg cobalt per day. | *Urinary cobalt levels*<br>64.3 (45–102) {3}<br>45.1 (31–56) {4}<br>6.4 (2.5–11.1) {3}<br>11.7 (5.5–25) {5}<br>11.3 (8.1–14.4) {2}<br>4.6 (0.3–13.6) {5}<br>*Serum cobalt levels*<br>18.3 (9.6–32) {3}<br>11.5 (10.4–12.9) {4}<br>2.0 (< 0.3–4.4) {3}<br>2.5 (1.4–4.4) {5}<br>3.5 (2.2–4.8) {2}<br>< 0.3 (< 0.3) {5} | Biological data are specific for employees who performed grinding operations, although air data reflect dust samples taken from various parts of the factory. The authors compared these levels to reference values for non-exposed persons( 0.0–2.0 μg/g creatinine) and noted that clear evidence of cobalt exposure. Exposure data from grinding operations are presented in Table B-2 | Posma and Dijstelberger *et al.* 1985<br>(The Netherlands, NR) |
| Powder handlers<br>Rubber press operators<br>Automatic press operators<br>Shapers (lathing)<br>Shapers (sawing)<br>Sintering workers<br>Workers using respirators<br>Office workers | 186 (110–262) {2}<br>367 (92–859) {6}<br>56 (9–210) {11}<br><br>33 (15–62) {7}<br>50 (8–144) {21}<br>28 (4–145) {21}<br>317 (7–1,203) {25}<br><br>NA | *Urinary cobalt levels*<br>148 (138–158) {2}<br>235 (41–392) {6}<br>34 (4–73) {11}<br><br>33 (11–95) {7}<br>41 (6–266) {21}<br>10 (2–46) {21}<br>26 (1–119) {25}<br><br>2 (1–4) {20} | *Blood cobalt levels (μg/dL)*<br>1.08 (0.88–1.28) {2}<br>1.87 (0.4–5.3) {6}<br>0.57 (0.1–0.95) {11}<br><br>0.67 (0.14–1.34) {7}<br>0.52 (0.15–1.15) {21}<br>0.26 (0.09–0.45) {21}<br>0.65 (0.2–3.9) {25}<br><br>0.19 (0.08–0.4) {20} | Ichikawa *et al*. 1985 (Japan, NR) |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m³ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Hand pressing<br>Automatic pressing<br>Forming<br>Sintering<br>Finishing (testing)<br>Maintenance | maximum > 100 {NR}<br>maximum > 10 {NR}<br>maximum > 50 {NR}<br>maximum < 10 {NR}<br>maximum > 10 {NR}<br>maximum > 50 {NR} | Mon.: up to 36 {26}<br>Fri.: up to 63 {26} | Air levels are maximum concentrations from histogram that showed percentage of samples at certain levels. Urine levels estimated from scatterplot of all samples. Article did not provide matched air and urinary data. | Scansetti *et al.* 1985 (Italy, NR) |
| Plant A<br>Weighing & mixing<br>Milling<br>Drying<br>Pressing<br>Machining<br>Reclaiming<br>Plant B<br>Weighing & mixing<br>Milling<br>Drying<br>Pressing<br>Machining<br>Reclaiming | <br>32,470 (44–438,000) {18}<br>8,661 (91–48,148) {13}<br>235 (100–375) {4}<br>755 (13–7,359) {14}<br>94 (2–336) {21}<br>671 (189–1,708) {7}<br><br>327 (20–1,480) {17}<br>282 (15–800) {6}<br>337 (36–640) {6}<br>326 (40–769) {9}<br>116 (7–504) {12}<br>214 (114–342) {11} | NA | Sampling was conducted in a manner to obtain peak exposure levels. Authors noted that they found peak air concentrations of cobalt exceeding 500 μg/m³ during many major steps in the production of cemented carbides. Data for grinding operations provided in Table B-2 | Sprince *et al.* 1984 (United States, NR) |
| Producing cobalt powder<br>Producing presintered tungsten carbide<br>Using hard metal | NR (675–10,000) {NR}<br>NR (120–284) {NR}<br>NR (180–193) {NR} | 35.1 (NR) {NR}<br>9.6 (NR) {NR}<br>11.7 (NR) {NR} | No additional information provided | Pellet *et al*. 1984 as cited in Angerer and Heinrich 1988 (NR, NR) |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m³ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Powder mixing<br>Pressing<br>General maintenance | 48 (NR) {NR}<br>33 (NR) {NR}<br>25 (NR) {NR} | NA | Cobalt air concentration in worker's breathing zone. Maximum value detected was 170 μg/m³. | NIOSH 1981<br>(United States, 1977–1978) |
| *Cobalt*<br>Powder processing<br>Tool & die operations<br>Casting<br>Forming<br>*Tungsten*<br>Powder processing<br>Tool & die operations<br>Casting<br>Forming | <br>0–2,720 {NR}<br>10–230 {NR}<br>0–6,800 {NR}<br>10–1,750 {NR}<br><br>880–25,600 {NR}<br>NA<br>520–17,600 {NR}<br>80–26,700{NR} | NA | Presented is the full range across a varying number of studies presented for each process stage (source doesn't specify if the data presented is a range or a range of means).<br>A value of 32,500 mg/m³ was presented for tungsten in forming operations; however, due to a discrepancy in the text and table, the next highest value is presented. | NIOSH 1977<br>(United States, Austria, Switzerland, Sweden, former USSR, NR) |
| *General air samples*<br>Metal preparation<br>Forming<br>Sintering<br>*Press operations*<br>Slug presses<br>Blank presses<br>*Machine tool operations*<br>Lathes<br>Surface grinders<br>Milling<br>Drilling<br>Saws<br>Slicers<br>Pelletizers | <br>(NR) 0–140 {14}<br>(NR) 10–150 {16}<br>(NR) 5–140 {8}<br><br>(NR) 10–900 {8}<br>(NR) 0–400 {18}<br><br><br>(NR) 10–800 {12}<br>(NR) 0.0–800 {32}<br>(NR) 10 (for all samples) {3}<br>(NR) 0–100 {6}<br>(NR) 10–400 {10}<br>(NR) 10–4,600 {7}<br>(NR) 30–2,160 {6} | | Lowest detected level for metal preparation was 10 μg/m³<br><br>Detail on differences between the two types of presses not provided; lowest detected level for blank presses was 10 μg/m³<br><br>Machine tool operations are pre-sintering steps. The lowest detected level for surface grinding was 1 μg/m³ (see Table B-2 for exposure levels from post-sintering grinding operations) and the lowest detected level for drilling was 20 μg/m³. The second highest level for slicers was 800 μg/m³ and the second highest level for pelletizers was 250 μg/m³. | McDermott *et al*. 1971<br>(U.S., NR) |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m$^3$ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Packing | (NR) 10–250 {3} | | | |
| *Other operations* | | | No additional detail provided for what miscellaneous operations entailed | |
| Equipment cleaning | (NR) 40–820 {6} | | | |
| Ball-mill loading | 30 {1} | | | |
| Screening | (NR) 60–440 {10} | | | |
| Powder mixing | (NR) 10–800 {3} | | | |
| Miscellaneous | (NR) 10–6,700 {6} | | | |
| Powder processing | *Total dust, personal samples*<br>A: 14,000 (NR) {NR}<br>B: 13,600 (NR) {NR}<br>C: 10,600 (NR) {NR}<br>*Total dust, area samples*<br>A: 3,300 (NR) {NR}<br>B: 2,900 (NR) {NR}<br>C: 2,000 (NR) {NR}<br>*Cobalt, personal samples*<br>A: 1,670 (NR) {NR}<br>B: 1,050 (NR) {NR}<br>C: 1,640 (NR) {NR}<br>*Cobalt, area samples*<br>A: 120 (NR) {NR}<br>B: 220 (NR) {NR}<br>C: 160 (NR) {NR} | NA | A, B, and C represent 3 different U.S. cemented carbide plants. Data based on a total of 977 samples. | Fairhall *et al.* 1949 |
| Tool production | *Total dust, personal samples*<br>A: 5,000 (NR) {NR}<br>B: 1,800 (NR) {NR}<br>C: 1,000 (NR) {NR}<br>*Total dust, area samples*<br>A: 2,200 (NR) {NR}<br>B: 1,000 (NR) {NR} | | | |

| Stage of the hard-metal production process | Air Concentration Mean (Range) {N} μg/m$^3$ | Biological levels[a] Mean (range) [N] μg/L | Additional information | Reference (Location, year of measurement) |
|---|---|---|---|---|
| Tool production (continued) | C: 500 (NR) {NR}<br>*Cobalt, personal samples*<br>A: 230 (NR) {NR}<br>B: 80 (NR) {NR}<br>C: 50 (NR) {NR}<br>*Cobalt, area samples*<br>A: 70 (NR) {NR}<br>B: 30 (NR) {NR}<br>C: 10 (NR) {NR} | | | |

CoA = cobalt in ai;, CoB = cobalt in blood; CoH = cobalt in hair; CoN = cobalt in toenails; N = number of samples; NA = not assessed; NR = not reported; WA = tungsten in air; WB = tungsten in blood; WH = tungsten in hair; WN = tungsten in toenails.
[a] Urinary levels unless otherwise noted.
[b] μg/g creatinine.
[c] ng/g.
[d] Geometric mean.
[e] Median.

**Table B-2. Hard-metal exposure levels from grinding and sharpening operations (Step 3) (levels are for cobalt unless otherwise noted)**

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Dry grinding<br><br>Area located near dry-grinding operations | Dust: 128 μg/m$^3$ {1}<br>Cobalt: 1 μg/m$^3$ {1}<br>Dust: 229 μg/m$^3$ {1}<br>Cobalt: 1 μg/m$^3$ {1} | NA | Respiratory mass fraction was reported to be 37% for dry grinding and 34% for the area next to the grinder: these were the highest respiratory mass fractions found in the study; however, the cobalt concentrations were the lowest of all work areas. Results for other work areas in the plant are reported in Section 2.5.2. | Stefaniak *et al.* 2007<br>(United States, NR) |
| (A) Powder mixing or dry-grinding<br>(B) Powder mixing or dry-grinding<br>(C) Grinding | *Cobalt*[b]<br>(A) 8.25[c] (0.1–16.4) {NR}<br>(B) 8.45[c] (0.9–16.0) {NR}<br>(C) 26.0[c] (14.6–37.4) {NR}<br>*Tungsten*[b]<br>(A) < 0.01[c] {NR}<br>(B) 0.1[c] (0.01–0.2) {NR}<br>(C) 3.0[c] (1.1–4.9) {NR} | *Cobalt*[d]<br>(A) [1.5[c] (0.9–2.8)[e]] {10}<br>(B) [26[c] (8.4–190)[e]] {11}<br>(C) [9.8[c] (3.7–25.6)[e]] {12}<br>(D) [0.05[c] (0.03–0.2)[e]] {16}<br>*Tungsten*[d]<br>(A) [< 0.1[c] (< 0.1–1.6)[e]] {10}<br>(B) [2.0[c] (1.0–8.0)[e]] {11}<br>(C) [13.4[c] (5.2–26.4[e])] {12}<br>(D) [< 0.1[c] (< 0.1–2.5)[e]] {16} | Groups A, B, and C reflect workers from three different factories. Groups A and B were exposed either to Co and WC powders through powder mixing or from dry-grinding activities (data not segregated for the two types of exposure). Group C exposed only from grinding activities.<br>For urine analysis, group D was a control group consisting of non-exposed workers.<br>Urinary levels presented for end-of-shift, and in units of μmol/mol creatinine in source paper with conversion units provided by authors. | Goldoni *et al.* 2004<br>(Italy, NR) |
| Wet and dry grinding operations | *Cobalt*<br>Wet: 0.2 {1}<br>Dry: 0.48 {1}<br>*Tungsten*<br>Wet: 3.3 {1}<br>Dry: 81.3 {1} | *Cobalt*<br>2.2 (0.19–6.0) {5}<br>*Tungsten*<br>94.4 (10.6–168.6) {5} | Air levels measured using personal sampling. Type of grinding process not specified for urine analysis results. | Kraus *et al*. 2001<br>(Germany, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Hard-metal and stellite[f] saw-blade grinding, brazing, and welding | *Before ventilation installed*<br>51–146 (10–346) {12}<br>*After ventilation installed*<br>8–26 (3–63) {41} | NA | Data presented here are for 4 workers who were involved in hard-metal grinding operations; however, they also performed grinding and other operations on steel and stellite[f] products.<br>Presented are the range of means and full range across the 4 workers | Simcox *et al.* 2000<br>(United States, 1995) |
| Grinding hard-metal and stellite[f] blades | NR ([1–70]) {91} | 14.2 (0.5–160) {131} | Measurements from 16 workplaces. Air range estimated from graph. | Linnainmaa and Kiilunen 1997<br>(Finland, NR) |
| Tool manufacturing and blade repair | Dust: 1,200[g] (300–10,400) {87}<br>Cobalt: 17[g] (2–240) {87} | NA | These results include data for grinding of stellite[f]. Authors noted that the respirable portion of total dust was high (48%–83%) (the low end [48%] was for stellite grinding). | Linnainmaa *et al.* 1996<br>(Finland, NR) |
| Blasting<br>Electron discharging<br>Grinding | 2 (1–4) {7}<br>3 (1–12) {18}<br>45 (1–482) {517} | NA | See Table B-1 for production exposure levels from this study. | Kumagai *et al.* 1996<br>(Japan, NR) |
| Grinding | (3) 31 (21–40) {3}<br>(4) 6 (2–12) {10} | *Urine*<br>(3) 29 {1}<br>(4) 9 {1}<br>*Blood*<br>(3) 0.40 (μg/dL) {1}<br>(4) 0.32 (μg/dL) {1}<br>*Hair*<br>(3) 9.11 (ppm) {1}<br>(4) 3.42 (ppm) {1} | Data are for two grinders from a study of 4 subjects with occupational asthma. Exposure levels for subjects 1 and 2, who performed tasks related to shaping and sintering, are presented in Table B-1 | Kusaka 1996<br>(Japan, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Grinding hard-metal blades | *Before*<br>(A) NR (9–39) {15}<br>(B) NR (16–160) {8}<br>(C) NR (6–33) {21}<br>(D) NA<br>(E) NR (3–91) {25}<br>(F) NR (1–7) {18}<br>*After*<br>(A) NR (< 2) {12}<br>(B) NR (< 3) {6}<br>(C) NR (3–15) {6}<br>(D) NR (< 1) {3}<br>(E) NR (12–27) {7}<br>(F) NR (2–28) {9} | *Before*[h]<br>(A) NR (9.2–17) {5}<br>(B) NR (8.4–19) {3}<br>(C) NR (26–44) {6}<br>(D) NA<br>(E) NR (6.1–63) {10}<br>(F) NR (13–15) {2}<br>*After*[h]<br>(A) NR (0.4–3.1) {9}<br>(B) NR (0.5–0.6) {2}<br>(C) 13 {1}<br>(D) 1.8 {1}<br>(E) NR (11–62) {5}<br>(F) NR (18–27) {2} | "Before" and "After" refer to before and after engineering controls installed.<br>Designations of A through F refer to different facilities that were assessed. | Linnainmaa 1995 (Finland, NR) |
| Grinding of hard-metal and stellite[f] saws | 9 (< 0.64–106) {278} | NA | Air levels were calculated using only the 62 measurements that were above the detection limit of 0.64 μg/m$^3$.<br>Data are from personal sampling from 112 workers. | Teschke *et al.* 1995 (Canada, 1991) |
| Grinding operations during hard-metal tool manufacturing | [89.5] (26.4–202.8) {10} | NA | A follow-up analysis, after ventilation was installed, showed reductions in cobalt air levels of roughly 1–3 orders of magnitude. | Paulsen and Kilens 1994, NR) |
| Grinding during diamond abrasive production (6 factories)<br>Grinding hard metal tools (23 factories) | S: 22[c] (15–45) {NR}<br>P: 230[c] (82–690) {NR}<br><br>S: 5[c] (2.5–94) {NR}<br>P: 9.3[c] (1.5–178) {NR} | 151 (34–520) {NR}<br><br>31.5 (0.8–730) {NR} | A total of 250 air samples and greater than 600 biological samples taken for this study (data for non-grinding operations presented in Table B-1); however, number of samples not provided for specific subgroups. | Mosconi *et al.* 1994 (Italy, 1991) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Wet and dry grinding and sharpening | 0.0036–0.350 (NR) {23} | 0–40.25 (0–86) {48} | Analysis of 12 manufacturing facilities. For air levels, mean data presented for 10 facilities. For urinary data, range of mean data and full range across all 12 facilities presented. | Imbrogno and Alborghetti 1994 (Italy, NR) |
| Wet grinding of hard-metal tools (3 factories) | **Factory A**<br>*Before*<br>Mon.: 376[g] ± 2.2[i] {10}<br>Fri.: 91[g] ± 2.4[i] {10}<br>*After*<br>Mon.: NA<br>Fri.: 9.9[g] ± 1.5[i] {10}<br>**Factory B**<br>Mon.: 8.7[g] ± 3.9[i] {10}<br>Fri.: 19.1[g] ± 2.8[i] {10}<br>**Factory C**<br>Mon.: 13.1[g] ± 1.8[i] {6}<br>Fri.: 6.4[g] ± 3.5[i] {4} | **Factory A**<br>*Before*<br>Mon.: 138.3 ± 108[j] {3}<br>Fri.: 123.7 ± 74[j] {3}<br>*After*<br>Mon.: NA<br>Fri.: NA<br>**Factory B**<br>Mon.: 15.3 ± 7.7[j] {5}<br>Fri.: 24.4 ± 14.1[j] {5}<br>**Factory C**<br>Mon.: 48.2 ± 7.3[j] {3}<br>Fri.: 74.7 ± 13[j] {3} | Factories A, B, and C refer to three different facilities that performed wet-grinding of hard-metal tools.<br>"Before" and "After" are in reference to measurements taken before and after installation of a ventilation system.<br>"Mon." and "Fri." refer to measurements taken on Monday and Friday of the same week. | Sesana *et al.* 1994 (Italy, NR) |
| Hard-metal tool grinding facilities | *Without*<br>P: 91[g] (5.0–1,338) {51}<br>S: 40[g] (5.0–110) {52}<br>*With*<br>P: 9[g] (1.0–38) {55}<br>S: 12[g] (4.0–58) {47} | NA | "With" and "Without" refer to facilities with and without ventilation systems.<br>"P" is for personal monitoring and "S" is for stationary monitoring across 11 small plants that performed grinding operations on hard-metal tools. | Sala *et al.* 1994 (Italy, NR) |
| Hard-metal manufacturing plant sharpening operations | 10[g] (4–70) {15} | NA | Exposure levels for workers engaged in mixing, forming, and pressing operations provided in Table B-1 | Sala *et al.* 1994 (Italy, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Grinding/sharpening of hard-metal tools | NA | 17 nmol/mmol CR {~150} | | White and Dyne 1994 (United Kingdom, NR) |
| 16 small "Widia" (hard metal) tool grinding facilities | *Without*<br>F: 6.68[g] ± 2.27[i] {16}<br>P: 47.75[g] ± 3.53[i] {18}<br>*With*<br>F: 3.47[g] ± 2.15[i] {6}<br>P: 4.43[g] ± 2.7[i] {17} | 28.5[g] ± 3.97[i] {6}<br><br><br>2.66[g] ± 1.69[i] {8} | "With" and "without" refer to the use of machines with aspirators.<br>"F" and "P" refer respectively to the use of fixed or personal monitoring methods. | Cereda *et al*. 1994 (Italy, NR) |
| Grinding (across 2 factories and 3 datasets) | *Cobalt*<br>S: 64–245 (NR) {NR}<br>P: 288–985 (NR) {NR}<br>< 7 μm: 4–14 (NR) {NR}<br>*Tungsten*<br>S: 2.1–62 (NR) {NR}<br>P: 22–77 (NR) {NR}<br>< 7 μm: 0.13–2.4 (NR) {NR} | CoB 45.6 (1–245) {88}<br>CoU 303.6 (0.75–5,500) {88}<br>CoH 49,088 (110–910,000)[k] {90}<br>CoN 53,792 (109–580,000)[k]{92}<br>WB 1.2 (0.04–6.5) {43}<br>WU 6.7 (0.11–230) {78}<br>WH 2,147 (25–59,000)[k] {75}<br>WN 3,056 (27–105,000)[k] {82} | "S" = stationary sampling<br>"P" = personal sampling.<br>< 7 μm is the concentration in the air fraction measuring less than 7 μm (considered respirable) measured by stationary sampling.<br>Biological data were aggregated and summarized across all workers irrespective of production stage or factory.<br>Exposure levels for workers involved in weighing operations presented in Table B-1 | Sabbioni *et al.* 1994a (Bergamo Province, Italy, NR) |
| Tip grinding operations in the production of carbide-tip saw blades | (A)<br>*Total cobalt*<br>[33.2] (NR) {6}<br>*Total tungsten*<br>NR (410–710) {3}<br>(B)<br>*Total cobalt*<br>27–73 (NR) {24}<br>*Respirable cobalt*<br>11 (2–28) {24} | *Overall*<br>NR (2.6–38) {13}<br>*Wet-grinding operations*<br>33.6 ± 6.5[j] {2}<br>*Dry-grinding operations*<br>12.2 ± 6.2[j] {4} | Group A consisted of area and personal samples of wet and dry grinding for cobalt, and area samples of wet and dry grinding for tungsten.<br>Group B consisted of area sampling of 4 locations over 6 shifts. For total Co, the range of the means for the four locations is provided (overall mean and range not reported). For respirable Co, overall mean and range for all 24 samples provided.<br>Group C provides the means of two sets of 4 personal samples for total cobalt. | Stebbins *et al.* 1992 (United States, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| | (C)<br>54 & 58 (NR) {8}<br>(D)<br>[87.4] (50–194) {5} | | Group D data are results for 5 single, personal air samples for total cobalt.<br>Overall urine analysis included hammering, brazing, and wet- and dry-grinding workers. | |
| Hard-metal factory grinding operations | 32 (1–440) {133} | NA | Authors noted that 66% of total dust was respirable (< 7 μm), and 70.1% of total cobalt was respirable. | Kusaka *et al*. 1992<br>(Japan, NR) |
| Four workers involved in sharpening and grinding operations | NA | *Urine*<br>(1) [5.0] (2.5–8) {3}<br>(2) 20 {1}<br>(3) 35 {1}<br>(4) 15 {1}<br>*Blood*<br>(1) [4.27] (1.5–9) {3}<br>(2) 4 {1}<br>(3) 4.9 {1}<br>(4) 2.5 {1}<br>***Tungsten***<br>*Urine*<br>(1) [347] (2–1,000) {3}<br>(2) 60 {1}<br>(3) 30 {1}<br>(4) 20 {1}<br>*Blood*<br>(1) [20.73] (0.9–60) {3}<br>(2) 0.7 {1}<br>(3) 1.0 {1}<br>(4) 0.9 {1} | Worker #1 developed terminal hard-metal pneumoconiosis and measurements were taken at admission, 4 months after admission, and 8 months after admission.<br>Authors noted that tungsten in blood and urine, and particularly in pubic hair and toenails of the patients was significantly higher than normal values and that this was a clear indication of exposure to occupational hard-metal dust. | Della Torre *et al*. 1990<br>(Italy, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Grinding, sharpening, and tooling of hard metals | *Respirable*<br>4 (ND–4) {31}<br>*Total*<br>30.2 (ND–97) {33} | NR (ND–7.6) (63} | Air levels include both personal and stationary monitoring results.<br>Means for air levels were calculated from only the data above the detection limit (only 1 sample above detection for respirable cobalt).<br>Only 30% of urine samples exceeded the detection limit of 3.4 μg/L. | NIOSH 1988<br>(United States, NR) |
| Saw blade and tool sharpening | *Cobalt*<br>(A) [45] (26–63) {2}<br>(B) [9.38] (2.8–14) {4}<br>(C) 30 {1}<br>*Tungsten*<br>(A) [645] (365–925) {2}<br>(B) [186] (ND–261) {4}<br>(C) NA | *Cobalt*<br>*Pre-shift urine sample*<br>(A) [13.5] (ND–19.1)[d] {8}<br>(D) [7.2] (4.9–9.5)[d] {4}<br>(E) [2.74] (1.8–4.1)[d] {12}<br>*Post-shift urine sample*<br>(A) [18.3] (12.9–23.8)[d] {8}<br>(D) [7.6] (7.2–8.0)[d] {4}<br>(E) [6.0] (2.6–13.2)[d] {12}<br>*Tungsten*<br>NA | Group A consisted of personal air and urine samples from two employees who performed wet and dry grinding. Group A's mean urine level was calculated from only samples above the level of quantitation. For Group A, the employee with the highest air levels also had the highest urinary levels.<br>Group B consisted of 4 area samples. For tungsten, the mean was calculated from the 3 values that were above the limit of quantitation.<br>Group C was a single measurement for cobalt from the outlet of an exhaust system that filtered and recirculated air in the workshop.<br>Group D was one truck driver who spent several hours per day in the workshop.<br>Group E was a control group of office workers. | NIOSH 1987c<br>(United States, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Finish grinding of hard-metal cutting tool inserts | *Respirable cobalt*<br>[4.3] (ND–8.4) {24}<br>*Total cobalt*<br>13.5 (ND–26.8) {24}<br>*Tungsten*<br>280 (ND–410) {24} | *Pre-shift*<br>10.5 (4.7–19)[d] {10}<br>*Post-shift*<br>18.09 (8.4–27.7)[d] {10} | Mean air levels were calculated from only the values above the detection limit.<br>The 10 urine samples were from 10 workers with personal air monitoring data. All 10 had pre- to post-shift increases in urinary cobalt. Respirable airborne cobalt was significantly associated with post-shift urinary cobalt levels ($P$ = 0.003). [Tungsten in air assumed total.] | NIOSH 1987b<br>(United States, NR) |
| Blasting<br>Electron discharging<br>Grinding<br>wet<br>dry | 3 (1–4) {5}<br>4 (1–5) {5}<br><br>53 (11–1,247) {205}<br>1,292 (1,113–1,471) {2} | NA | The authors noted that the high levels for the dry grinder decreased to 14 μg/m$^3$ with the installation of a local ventilation system.<br>Exposure data for workers engaged in powder production, pressing, shaping, and sintering are provided in TableB-1 | Kusaka *et al*. 1986b (Japan, 1981–1984) |
| Hard metal tool factory | (A) 44 (4–227) {27}<br>(B) 45 (3–161) {18}<br>(C) 92 (15–291) {12}<br>(D) 44 (3–205) {25}<br>(E) 317 (7–1,203) {25}<br>(F) NA | *Urine*<br>(A) 35 (2–180) {27}<br>(B) 19 (2–67) {18}<br>(C) 68 (3–265) {12}<br>(D) 17 (1–69) {25}<br>(E) 26 (1–119) {25}<br>(F) 2 (1–4) {20}<br>*Blood*<br>(A) 4.2 (1.0–13) {27}<br>(B) 3.3 (1.6–5.2) {18}<br>(C) 4.3 (1.2–19) {12}<br>(D) 3.5 (1.0–10) {25}<br>(E) 6.5 (2–39) {25}<br>(F) 1.9 (0.8–4.0) {20} | "A" through "D" refer to 4 groups of wet grinders who were grouped based on type of work or location.<br>"E" is a group of workers who used respirators.<br>"F" was a group of office workers used as unexposed controls.<br>Exposure levels for workers performing other tasks presented in Table B-1 | Ichikawa *et al.* 1985<br>(Japan, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Grinding operations in a hard-metal factory | *Dust*<br>4.3 (0.3–15) mg/m$^3$ {NR}<br>*Cobalt*<br>cobalt content ranged from 4% to 17%; (authors noted a daily load of about 3 mg cobalt per day) | 25.5 (5.8–39)[d] {10} | Biological data are specific for employees who performed grinding operations, although air data reflect dust samples taken from various parts of the factory (not just grinding operations). The authors compared these levels to reference values for non-exposed persons 0.0–2.0 μg/g creatinine and noted that clear evidence of cobalt exposure. Exposure data from other operations are presented in Table B-1 | Posma and Dijstelberger 1985 (The Netherlands, NR) |
| Grinding operations at 2 hard-metal production facilities | 118 (12–307) {5}<br>17 (3–81) {8} | NA | Sampling was conducted in a manner to obtain peak exposure levels. Exposure levels for other production stages presented in Table B-1 | Sprince *et al.* 1984 (USA, NR) |
| Grinding operations in a hard-metal plant | *Dust*<br>2,100 (1,500–3,000) {4}<br>*Cobalt*<br>7%–9% of dust concentration<br>*Tungsten*<br>66%–73% of dust concentration | NA | Only cobalt and tungsten content of dust presented (concentration not presented); range is based on results from two analytical techniques. | Koponen *et al.* 1982<br>(Finland, NR) |
| Grinding operations at hard-metal plants | 19 (NR) {NR} | NA | Exposure levels for other production stages presented in Table B-1 | NIOSH 1981<br>(NR, 1977–1978) |
| Dry grinding without exhaust | NR (40–2,440) {NR} | NA | No additional information provided | NIOSH 1977<br>(Switzerland, NR) |

| Operation | Air concentration Mean (Range) {N} (μg/m$^3$) | Biological Levels[a] Mean (Range) {N} (μg/L) | Additional information | Reference (location, year of measurement) |
|---|---|---|---|---|
| Wet grinding of hard-metal tools | *Cobalt*<br>S: 280 (40–930) {25}<br>P: 240 (30–560) {12}<br>*Tungsten*<br>S: 5,160 (< 200–12,800) {25}<br>P: 3,930 (720–8,060) {12} | NA | "S" is for stationary sampling and "P" is for personal sampling results<br>A small follow-up study after ventilation controls installed showed cobalt levels below detection limits | Lichtenstein 1975 (United States, NR) |

CoA = cobalt in air; CoB = cobalt in blood; CoN = cobalt in toenails; CoH = cobalt in hair; CR = creatinine; N = number of samples; NA = not assessed; ND = not detected (below the limit of quantitation); NR = not reported; WA = tungsten in air; WB = tungsten in blood; WH = tungsten in hair; WN = tungsten in toenails.

[a] Urinary levels unless otherwise noted.

[b] In the original article, units were incorrectly stated to be mg/m$^3$ rather than μg/m$^3$ (personal communication from A. Mutti).

[c] Median.

[d] μg/g creatinine.

[e] Interquartile range.

[f] See glossary for definition of stellite. The exposure data reported includes combined data for both stellite and cobalt–tungsten carbide hard metals.

[g] Geometric mean.

[h] Original data in units of nmol/L, converted to μg/L using the conversion factors 1 nmol/L = 58.9 ng/L (Goldoni *et al.* 2004), and 1 ng/L = 0.001 μg/L.

[i] Geometric standard deviation.

[j] Standard deviation.

[k] ng/g.

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