Report on Carcinogens
## Draft Background Document for

Cobalt–Tungsten Carbide Powders and Hard Metals

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U.S. Department of Health and Human Services
Public Health Services
National Toxicology Program
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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 may 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 (DHHS), 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chemical and physical properties, analytical methods, production, use, and occurrence may come from published and/or unpublished sources. The NTP will provide a reference for all published and unpublished sources used in this document.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 nominations 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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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:

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.

1 Executive Summary

2 **Introduction**

3 The combination of cobalt and tungsten carbide occurs primarily in powders and hard

4 metals or cemented (i.e., sintered) carbides. Cobalt–tungsten carbide hard metals are

5 composites of carbides (including tungsten carbide alone or in combination with small

6 amounts of other carbides) with a metallic cobalt binder, pressed into a compact, solid

7 form at high temperatures by a process known as "sintering." This nomination includes

8 cobalt–tungsten carbide powders and dusts (both unsintered and sintered) and cobalt–

9 tungsten carbide hard metals. Cobalt–tungsten carbide hard metals have properties of

10 extreme hardness, abrasion resistance, and toughness and are used primarily in cutting

11 tools and wear-resistant machine parts.

12 In 2003, the International Agency for Research on Cancer (IARC) reviewed the

13 carcinogenicity of metallic cobalt particles, with or without tungsten carbide, and cobalt

14 sulfate and other soluble cobalt (II) salts. IARC concluded that there was limited

15 evidence in humans for the carcinogenicity of cobalt metal with tungsten carbide, and the

16 overall evaluation was that cobalt metal with tungsten carbide was *probably carcinogenic*

17 *to humans* (Group 2A).

18 **Human Exposure**

19 Cobalt–tungsten carbide hard metal is used primarily in cutting tools, to machine

20 tempered steel, in rock drilling bits, and in a variety of tools. It is produced by preparing

21 tungsten carbide from tungsten metal or tungsten oxide and carbon, adding a mixture of

22 powdered cobalt metal and other compounds to produce cobalt–tungsten carbide

23 powders, which are then pressed, shaped, sintered, and finished as hard-metal products.

24 Total U.S. domestic production of hard-metal products was estimated at 5,527 metric

25 tons [6,080 tons] in 2004, and the USGS estimated that 6,610 metric tons [7,286 tons] of

26 tungsten and 792 metric tons [873 tons] of cobalt were used in the production of

27 cemented carbides in the United States in 2007.

1   Workers potentially are exposed to respirable dusts at many points during the

2   manufacturing process. Exposure can be assessed by measuring ambient air

3   concentrations of cobalt or tungsten or by biological monitoring, including measurements

4   of cobalt or tungsten in urine, blood, tissues, or exhaled air. Exposure generally is highest

5   among workers handling hard metal in powder form before or during the sintering

6   process (Step 2). Exposure can also occur during the grinding or sharpening of hard-

7   metal blades (Step 3) and from other processes. Historically, exposure levels from

8   production have decreased over time, possibly as a result of improved industrial hygiene

9   in hard-metal producing factories.

10   The potential exists for general-population exposures to cobalt–tungsten carbide hard-

11   metal powders for persons living near facilities that manufacture or process hard metal or

12   hard-metal products. There is one OSHA regulation specific to cemented tungsten

13   carbide (a synonym for hard metals), although there are numerous other regulations for

14   cobalt and tungsten metals and compounds. Similarly, there is one guideline for cemented

15   tungsten carbide and numerous guidelines for cobalt and tungsten metals and compounds.

16   **Human Cancer Studies**

17   Workers in the cobalt–tungsten carbide powders and hard-metal (hereafter called hard

18   metals) industry are exposed to either presintered or sintered hard-metal particles. Four

19   cohort studies (although not mutually independent) were identified that evaluated

20   exposure to cobalt–tungsten carbide powders and hard metals and cancer mortality. These

21   studies included (1) a cohort study of Swedish workers at three hard-metals facilities

22   (Hogstedt and Alexandersson 1990), (2) a small cohort of French hard-metal

23   manufacturing workers (Lasfargues *et al.* 1994), (3) a multi-plant cohort study of workers

24   at 10 hard-metal producing factories in France, which also included a nested case-control

25   analysis (Moulin *et al.* 1998), and (4) a cohort study of the largest factory of the multi-

26   plant French study (Wild *et al.* 2000). The multi-plant study also included workers

27   studied by Lasfargues *et al.* All of the studies attempted to evaluate exposure-response

28   relationships, although the exposure assessments by Hogstedt and Alexandersson and

1   Lasfargues *et al.* were crude. Both Wild *et al.* and Moulin *et al.* attempted to control for

2   smoking and/or other occupational exposure.

3   All four studies reported an increased lung cancer risk, with significantly increased lung

4   cancer mortality either in the whole cohort or among workers with higher or longer

5   exposure, or longer latency. Hogstedt and Alexandersson found significant excess lung

6   cancer mortality in a subgroup of long-latency, long-exposure–duration workers, and

7   Lasfargues *et al.* found a five-fold significantly elevated SMR in their high-exposure

8   group. Moulin *et al.* (1998) found an overall increase in lung cancer mortality of

9   borderline statistical significance and a significantly increased risk for exposure levels

10 higher than level 2 compared with the lowest level. In the nested case-control study, the

11 risk of lung cancer increased significantly with duration of exposure ($P = 0.03$) and

12 cumulative dose (unweighted) ($P = 0.01$) and increased non-significantly with exposure

13 level ($P = 0.08$) and cumulative dose (frequency weighted) ($P = 0.08$). Adjustment for

14 smoking or known or suspected carcinogens did not change the ORs. Wild *et al.* (2000)

15 found significantly elevated lung cancer SMRs among all workers and workers ever

16 employed in pre-sintering workshops, and among the highest exposure category

17 (exposure score, unweighted cumulative exposure, weighted cumulative exposure) to

18 hard metal dusts. In models controlling for smoking and exposure to any "IARC

19 carcinogen" (PAHs, silica, nickel compounds, chromium compounds, or cobalt without

20 tungsten), the test for trend was of borderline significance for exposure duration and was

21 not significant for exposure level or cumulative dose. In analyses that evaluated exposure

22 to unsintered hard metals, a significantly increased trend for duration of exposure was

23 found in models that controlled for smoking and exposure to any "IARC carcinogen." No

24 increased risk for exposure to sintered metals was found in this model.

25 Hogstedt and Alexandersson was the only study to evaluate risks for tumors sites other

26 than lung in more detail, such as evaluation of risks by exposure groups, exposure

27 duration, and individual factory. They reported a significant excess risk for leukemia

28 among workers employed at one of the factories and exposed for less than 5 years, but

29 not among longer exposed workers. A non-significant excess of leukemia was found

30 among the small cohort study of French workers (Lasfargues *et al.*), but not among the

1   larger studies (Moulin *et al.*, Wild e*t al.*). Non-significant excesses of cancer of the

2   esophagus (Lasfargues *et al.*, Moulin *et al.*, Wild *et al.*), upper gastrointestinal tract

3   (Moulin *et al.*, Wild *et al.*), and pleura (Moulin *et al.,* Wild *et al.*) were found in the

4   overlapping French studies.

5   **Studies in Experimental Animals**

6   No studies of the carcinogenicity of cobalt–tungsten carbide powders or hard metals in

7   experimental animals were identified.

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

9   Humans are exposed to cobalt–tungsten carbide hard-metal particles through inhalation

10   and dermal contact. Hard-metal particles of respirable size are potentially deposited

11   throughout the respiratory tract, including in the alveoli. Studies in humans and animals

12   have demonstrated that when cobalt–tungsten carbide hard-metal particles are deposited

13   in the lung, cobalt metal is rapidly solubilized, cleared from the lung, distributed in the

14   body, and excreted in urine, whereas tungsten carbide particles persist longer in lung

15   tissue. Rats administered cobalt–tungsten carbide intratracheally excreted significantly

16   greater amounts of cobalt in the urine as compared with rats administered cobalt metal,

17   suggesting that cobalt has a greater bioavailability when combined with tungsten carbide.

18   In hard-metal workers, cobalt has been detected in urine, whole blood, pubic hair, and

19   toenails, and tungsten has been detected in urine, feces, pubic hair, and toenails.

20   **Toxicity**

21   Cobalt–tungsten carbide hard-metal dust has been shown to be more toxic than pure

22   cobalt or tungsten carbide in the lungs of rats and *in vitro* in rodent cells (mouse

23   peritoneal macrophages and rat alveolar macrophages) and human cells (type II

24   pneumocytes). Occupational inhalation exposure to cobalt–tungsten carbide hard-metal

25   dust is associated in some workers with the occurrence of hard-metal disease, a giant-cell

26   interstitial pneumonia that can develop into pulmonary fibrosis, with a potentially fatal

27   outcome. Other toxic effects reported in hard-metal workers included contact dermatitis,

28   occupational asthma, and memory loss.

1 **Mechanistic and Genotoxicity Data**

2 Cobalt–tungsten carbide hard-metal particles have been shown to be more toxic than

3 cobalt or tungsten carbide individually in the lungs of rats and *in vitro* in rodent cells

4 (mouse peritoneal macrophages and rat alveolar macrophages) and human cells (type II

5 pneumocytes). Differences in cellular cobalt uptake alone cannot account for the greater

6 toxicity of cobalt–tungsten carbide hard-metal particles than pure cobalt. [Toxicity and

7 genotoxicity appear to be mediated both by solubilized cobalt ions and through a surface

8 chemistry reaction between cobalt and tungsten carbide that occurs at the particulate

9 level.] Several *in vitro* and *in vivo* studies have demonstrated that the interaction between

10 cobalt metal and tungsten carbide particles and molecular oxygen produces reactive

11 oxygen species, which are involved directly or indirectly (e.g., via a lipoperoxidation

12 process) in the genotoxicity of cobalt–tungsten carbide hard metals.

13 Genotoxicity studies have demonstrated that cobalt–tungsten carbide hard metals cause

14 DNA damage and micronucleus formation in human peripheral blood lymphocytes *in*

15 *vitro* and in type II pneumocytes (but not peripheral blood lymphocytes) of rats exposed

16 *in vivo*. A study evaluating the genotoxic effects of occupational exposure to cobalt–

17 tungsten carbide hard-metal particles did not find increased DNA damage or

18 micronucleus formation in blood lymphocytes of exposed workers. Cobalt–tungsten

19 carbide hard-metal particles caused significantly more (approximately threefold

20 increased) DNA breaks and micronuclei in cultured human lymphocytes than cobalt

21 particles alone.

22 Cobalt–tungsten carbide hard-metal carcinogenicity might also be mediated via the

23 release of cobalt ions. Cobalt ions contribute to aneugenic effects (as evident from

24 micronucleus formation) and inhibit DNA repair processes. Cobalt ions also have been

25 shown to modulate apoptosis, regulate genes involved in the response to hypoxia, and

26 replace or mimic essential divalent metal ions in proteins regulating cell-cycle control

27 and DNA repair, thus altering cellular reactions. Several cobalt compounds (cobalt

28 sulfate, cobalt chloride, and cobalt naphthenate) and cobalt metal cause tumors in

1   experimental animals. Cobalt sulfate is listed in the *Report on Carcinogens, Eleventh*

2   *Edition* as *reasonably anticipated to be a human carcinogen*.

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- 8th edition

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

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

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

WC: tungsten carbide

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1 Introduction

The combination of cobalt and tungsten carbide occurs primarily in powders and hard metals. 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 are composites of carbides with a metallic cobalt binder, pressed into a compact, solid form at high temperatures by a process known as "sintering." This nomination includes cobalt–tungsten carbide hard-metal powders and dusts (both unsintered and sintered) and hard metals. Cobalt–tungsten carbide hard metals are used primarily in cutting tools. Exposure to cobalt–tungsten carbide 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 cobalt–tungsten carbide 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   **1.1   Identification and physical-chemical properties**

2   "Hard metal" is a generic term for composite materials produced by powder metallurgy

3   and combining a carbide with a metallic binder. A composite is a material formed by

4   combining two or more materials present as distinct phases, so as to take advantage of

5   desirable properties of each component. In the case of hard metals, hard ceramic particles

6   (carbides) are present within a ductile-metal matrix material. Most commonly, hard

7   metals are composites of tungsten carbide (WC, including tungsten carbide alone or in

8   combination with small amounts of other carbides) and metallic cobalt (Kirk-Othmer

9   1997), and this nomination is specific for these types of hard metals and their powders.

10   Cobalt–tungsten carbide hard metals have properties of extreme hardness, abrasion

11   resistance, and toughness.

12   Cobalt–tungsten carbide hard metals were developed in Germany during and after World

13   War I and were first marketed commercially by a German company in 1927 as *Widia*

14   (wie Diamant or diamond-like), which consisted of tungsten carbide with 6% cobalt as a

15   binder (Brookes 1998, Upadhyaya 1998). Hard-metal production in Germany was highly

16   secretive, particularly during World War II. Following the end of that war, British

17   Intelligence published a report detailing German production techniques, control methods,

18   and research projects for hard metal, and this report was used by many hard-metal

19   manufacturers outside of Germany in the years following the war. Many developments in

20   the production of hard metals since World War II have taken place in the United States,

21   Austria, Sweden, Japan, and other countries. The secrecy that surrounded hard-metal

22   production techniques during and after World War II contributed to a continuing problem

23   of a lack of a single, uniform standard based on compositions and properties of hard

24   metals. As discussed further below, the existing coding systems are based on applications

25   for the products, and, as a result, many hundreds of potential compositions of cobalt,

26   tungsten carbide, and other metals and their carbides are manufactured by different

27   producers. As a result of these widely varying compositions, no uniform set of physical-

28   chemical properties can be defined for the mixture of cobalt and tungsten carbide in hard

29   metals.

1 Cobalt–tungsten carbide hard metals have undergone many improvements, through

2 changes in manufacturing methods and materials (Kirk-Othmer 1997). The process

3 materials are fine powders, and cobalt–tungsten carbide hard-metal manufacture uses

4 powder metallurgy techniques. Tungsten carbide and cobalt form a solid through the

5 process of sintering: a mixture of tungsten carbide particles and powdered cobalt is

6 heated to between 1,350°C and 1,550°C, and the solid is formed through diffusion, which

7 may occur even at temperatures below the melting point of cobalt (1,495°C) (Kriz 2004).

8 Tungsten carbide is hard (able to resist cutting, abrasion, penetration, bending, and

9 stretching) but brittle; cobalt is soft but tough (able to withstand great strain without

10 tearing or breaking). Cobalt–tungsten carbide hard metals combine the hardness of

11 tungsten carbide with the toughness of cobalt. Their physical properties vary with the

12 relative proportions of cobalt, tungsten carbide, and other carbides and depend on the

13 following factors (Brookes 1998):

14   • compositions and relative proportions of the phases (e.g., metal and carbide);

15   • size, shape, and distribution of carbide particles;

16   • degree of intersolubility of carbides;

17   • excess or deficiency of carbon;

18   • variations in composition and structure caused by diffusion, precipitation, or
19   segregation;

20   • production methods generally, but especially milling, carburizing (production of
21   tungsten carbide from tungsten and carbon), and sintering methods, and the
22   choice of raw materials;

23   • post-sintering treatments, such as hot isostatic pressing; and

24   • coatings or diffusion layers applied or developed after initial sintering.

25 In general, the hardness and abrasion resistance of hard metals increase with decreasing

26 size of the tungsten carbide particles and decreasing cobalt content (provided that enough

27 cobalt is present to ensure complete liquid-phase sintering) (Brookes 1998).

1 The composition of commercial-grade cobalt–tungsten carbide hard metals can vary

2 greatly; it generally ranges from 50% to 97% tungsten carbide (along with other metallic

3 carbides such as titanium carbide or tantalum carbide; see Table 1-1) and from 3% to

4 16% cobalt, with variations in grain size and additives. The proportion of cobalt as the

5 binding metal in the composite hard metal is a function of the use of the material. For

6 cutting tools, when the major use is for coarse machining, the binding-metal content is

7 higher, to provide increased toughness, while for finish machining, the binding-metal

8 content is lower (Azom 2004).

9 There is no uniform system for assuring the composition of hard metals (MPR 2002);

10 several classification systems are accepted worldwide (Kirk-Othmer 1997, Upadhyaya

11 1998). One classification system for use as highly wear-resistant machine parts (wear

12 parts) is based on International Organization for Standardization (ISO) application codes.

13 However, a classification system for hard metals used for cutting tools has not been

14 successful, because of the importance of other physical properties (Kirk-Othmer 1997).

15 Table 1-1 shows representative compositions and physical properties of hard metals for

16 use as wear parts by ISO application code. The ISO application codes are for guidance

17 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/cm³)	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
    water
    nitric acid, hydrogen fluoride
	insoluble
	soluble
		NA
		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.

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 cobalt–tungsten carbide 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), biological indicators of exposure (Section 2.3), hard-metal manufacturing and occupational exposure (Section 2.4), environmental levels and general population exposure (Section 2.5), regulations and guidelines for cobalt–tungsten carbide powders and 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," "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 cobalt–tungsten carbide powders and 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).

1   **2.2   Production**

2   Worldwide use of cemented carbides has increased steadily over the years, from

3   approximately 10 tons in 1930 to approximately 30,000 tons per year in the early 2000s

4   (Azom 2004). From 1990 to 1996, 20 U.S. companies reported estimated production of at

5   least 10 metric tons [11 tons], with an average annual production of 147 metric tons [162

6   tons] per company (Brookes 1996). [However, many additional producers were identified

7   without any estimates of annual production. Therefore, the actual production level of

8   hard-metal containing cobalt and tungsten carbide was likely much higher.] In a public

9   comment received from Kennametal, Inc. in response to a *Federal Register* notice of

10   May 19, 2004 (FR 2004), Hsu (2004) reported that a USGS estimate from 2004 put the

11   total domestic (U.S.) production of hard metals products at 5,527 metric tons [6,080

12   tons]. The United States Geological Survey (USGS 2008a, 2008b) estimated that 792

13   metric tons [873 tons] of cobalt [9.3% of total U.S. cobalt consumption] and 6,610 metric

14   tons [7,286 tons)] of tungsten [56% of total U.S. tungsten consumption] were used in the

15   production of cemented carbides in the United States in 2007.

16   The Thomas Register (2008) identified 127 U.S. and Canadian companies that produced

17   or supplied cobalt–tungsten carbide and materials made from the compound. In 1996,

18   approximately 1,000 U.S. companies were identified as hard-metal producers or suppliers

19   (Brookes 1996); however, this figure included wholesalers and retailers of finished hard-

20   metal products. The Cemented Carbide Producers Association in the United States has 22

21   members or partner members (CCPA 2008). In 2007, the United States exported

22   approximately 1.3 million kilograms [1,427 tons] and imported approximately 1.6 million

23   kilograms [1,778 tons] of tungsten carbide (ITA 2008); however, no data were reported

24   specific to cobalt–tungsten carbide.

25   **2.3   Biological indicators of exposure**

26   The American Conference of Governmental Industrial Hygienists (ACGIH) lists both

27   urinary and blood concentrations of cobalt as biological determinants of exposure to that

28   element (see Section 2.7 for information on regulations and guidelines), but no

29   recommended biological exposure index (BEI) is listed for tungsten or cobalt–tungsten

1   carbide hard metals (ACGIH 2003). The BEIs for cobalt are 15 µg/L in urine and 1 µg/L

2   in blood, and are to be measured in end-of-shift, end-of-workweek samples.

3   Significant correlations between cobalt air levels and cobalt levels in blood and/or urine

4   have been found in several studies (Ichikawa *et al.* 1985, Lison *et al.* 1994, Sabbioni *et*

5   *al.* 1994a, Scansetti *et al.* 1985). No correlation between air and urinary cobalt levels was

6   found in two other studies by Scansetti *et al.* (1994, 1998), but the authors noted in the

7   first study that the choice of a mid-week day for sampling and the potential contribution

8   of skin or gastrointestinal absorption from the diry working conditions could have

9   presented a problem in determining an association, and in the second study they

10 considered the data too scanty to find any significant association. Ichikawa *et al.* 1985

11 found significantly higher blood and urine levels for exposed workers than for office

12 workers who were used as unexposed controls. They estimated that a cobalt exposure

13 level of 100 µg/m^3 corresponded with 95% confidence interval concentrations for cobalt

14 in blood of 0.57 to 0.79 µg/dL and in urine of 59 to 78 µg/L [creatinine values not

15 reported.] The relationships between cobalt concentration in the breathing zones and

16 those in blood and urine was linear and positive with significant correlations ($r = 0.96$, P

17 < 0.001 for blood and $r = 0.99$, $P < 0.001$ for urine). Sabbioni *et al.* (1994a) noted that

18 good correlations existed between cobalt in air and cobalt in urine or blood, but that these

19 correlations were more evident at lower concentrations than higher concentrations.

20 Sabbioni *et al.* also reported significant correlations for cobalt with tungsten in urine ($r =$

21 0.80, $P < 0.001$), in hair ($r = 0.45$, $P < 0.01$), and in blood ($r = 0.14$, $P < 0.01$). Scansetti

22 *et al.* (1985) reported significant correlations between cobalt in work-room air and urine

23 for 10 different (out of 15 total) comparisons between exposure (for either a single day or

24 the mean for a week) and urinary measurements (either beginning or end of shift).

25 Comparisons for Monday ($r = 0.831$, $P < 0.01$), Wednesday ($r = 0.364$, $P < 0.05$), and

26 Friday ($r = 0.351$, $P < 0.05$) between exposures for those days and end-of-shift urine

27 levels were all significant. Similarly, Lison *et al.* (1994) compared the log of air cobalt

28 concentrations with end-of-shift urinary cobalt levels for 10 hard-metals workers.

29 Significant correlations were found for both Monday ($r = 0.80$, $P < 0.005$) and Friday (r

30 $= 0.63$, $P < 0.03$).

1   Data also have been reported for tungsten in urine, which is another potential biomarker

2   for exposure (Goldoni *et al*. 2004, Kraus *et al*. 2001, Sabbioni *et al*. 1994a, Della Torre *et*

3   *al*. 1990). In an exposure assessment in a German hard-metal plant, Kraus *et al*. (2001)

4   examined the variation in species of tungsten, and hence its bioavailability, across the

5   different hard-metal production workshops (see Table 2-1 for tungsten exposure data).

6   Powder processing resulted in exposure to tungsten metal, while tungsten carbide was

7   identified during forming, pressing, and sintering. Production of tungsten carbide resulted

8   in exposure to tungsten metal and oxide in addition to the carbide. Grinding processes

9   involved exposures to tungstenate (WO_4^{2-} or tungstate) for wet grinding and tungsten

10 carbide and oxide for dry grinding. Tungsten bioavailability was reported to increase in

11 the order: tungsten metal, tungsten carbide, tungstenate [the ranking of tungsten oxide

12 was not provided].

13 Other biological media that have been explored as potential indicators of hard-metal

14 exposure include pubic hair, toenails, exhaled breath condensate (the fluid formed by

15 cooling exhaled air), lung tissue, and mediastinal lymph node tissue (Della Torre *et al*.

16 1990, Goldoni *et al*. 2004, Hillerdal and Hartung 1983, Mutti and Corradi 2006, Rizzato

17 *et al*. 1992, Sabbioni *et al*. 1994a, Sabbioni *et al*. 1994b, Sjogren *et al*. 1980). In general,

18 the authors of these studies proposed that cobalt (and tungsten in the Della Torre *et al*.

19 study) in these media could be used to assess chronic or past exposures.

20 **2.4   Hard-metal manufacturing and occupational exposure**

21 It is difficult to estimate the number of people in the United States who may be

22 occupationally exposed to hard metals; however, in a public comment received from

23 Kennametal, Inc. in response to a *Federal Register* notice of May 19, 2004 (FR 2004),

24 Hsu (2004) reported that Kennametal, as the largest U.S. hard-metal manufacturing

25 company (consuming an estimated 70% of the tungsten used for U.S. production of hard-

26 metal products), employed approximately 1,700 people in the manufacture of hard-metal

27 products. The number of employees at the companies manufacturing the remaining 30%

28 of hard-metal products is not known, but as noted above (Section 2.2), over 20 other U.S.

29 companies each manufactured at least 10 metric tons [11 tons] of hard metals in the early

30 1990s.

1   This section discusses the general stages associated with the production of hard metals

2   (Section 2.4.1), the chemical and physical characteristics of the hard-metal dusts across

3   the production process (Section 2.4.2), the processes involved in the recycling and

4   recovery of hard-metals (Section 2.4.3), occupational exposure for various manufacturing

5   processes (Section 2.4.4), exposure levels associated with Step 2 and other processes

6   (Section 2.4.5), exposure during finishing of sintered hard-metal products (Step 3)

7   (Section 2.4.6), exposure to end-users (other than grinders or sharpeners) (Section 2.4.7),

8   and non-process specific exposure data for hard-metal production (Section 2.4.8).

9   2.4.1   *Manufacturing processes*

10 Hard-metal manufacturing processes vary somewhat, but all have the same basic

11 elements involving production of cobalt and tungsten carbide powders followed by

12 mixing the powders and pressing into a compact, solid form and heating to a temperature

13 of approximately 1,500°C: a process known as "sintering." The process is illustrated in

14 Figure 2-1 and is divided into the following three steps representing different stages in

15 the manufacturing process: Step 1, producing the cobalt and tungsten carbide powders;

16 Step 2, mixing the powders, drying, pressing, presintering, shaping the presintered hard

17 metal, and sintering; and Step 3, finishing the sintered products.

18 Many variations exist for the manufacturing process, but generally, in a typical process,

19 the potential for exposure to cobalt–tungsten carbide begins when the sized and defined

20 cobalt and tungsten-carbide powders are weighed, mixed, and screened (Step 2 in Figure

21 2-1). The powder mixtures are then added to vessels containing organic solvents (usually

22 heptane or similar solvents) and further mixed and milled, and a binder such as paraffin

23 or polyethylene glycol is added. The slurry is dried and then molded into the general

24 shape of the final item by a number of process, such as hydrostatic, isostatic, or

25 mechanical pressing. At this point, the work pieces, held together by paraffin or similar

26 agents, are soft and easily machined. Parts may go directly to machining (e.g., with lathes

27 or milling machines) or may be presintered at 500°C to 800°C before machining. The

28 products are then sintered at high temperature (1,350°C to 1,550°C), which increases

29 diffusion between the binder metal and the carbide, eliminating voids and porosities in

30 the composite material, and removes the paraffin or other temporary binding agent.

1   Sintering is done in vacuum ovens and may be followed by hot isostatic pressing. After

2   sintering, parts may be sandblasted or shotblasted in conjunction with machining, usually

3   in glove boxes or hoods (Step 3 in Figure 2-1). Sintered parts typically are finished by

4   wet or dry grinding processes. In some cases, parts are surface-coated with materials such

5   as titanium nitride for increased wear resistance through chemical or physical vapor

6   deposition in a sealed reactor process (Kirk-Othmer 1997, Tucker Jr. 1996).
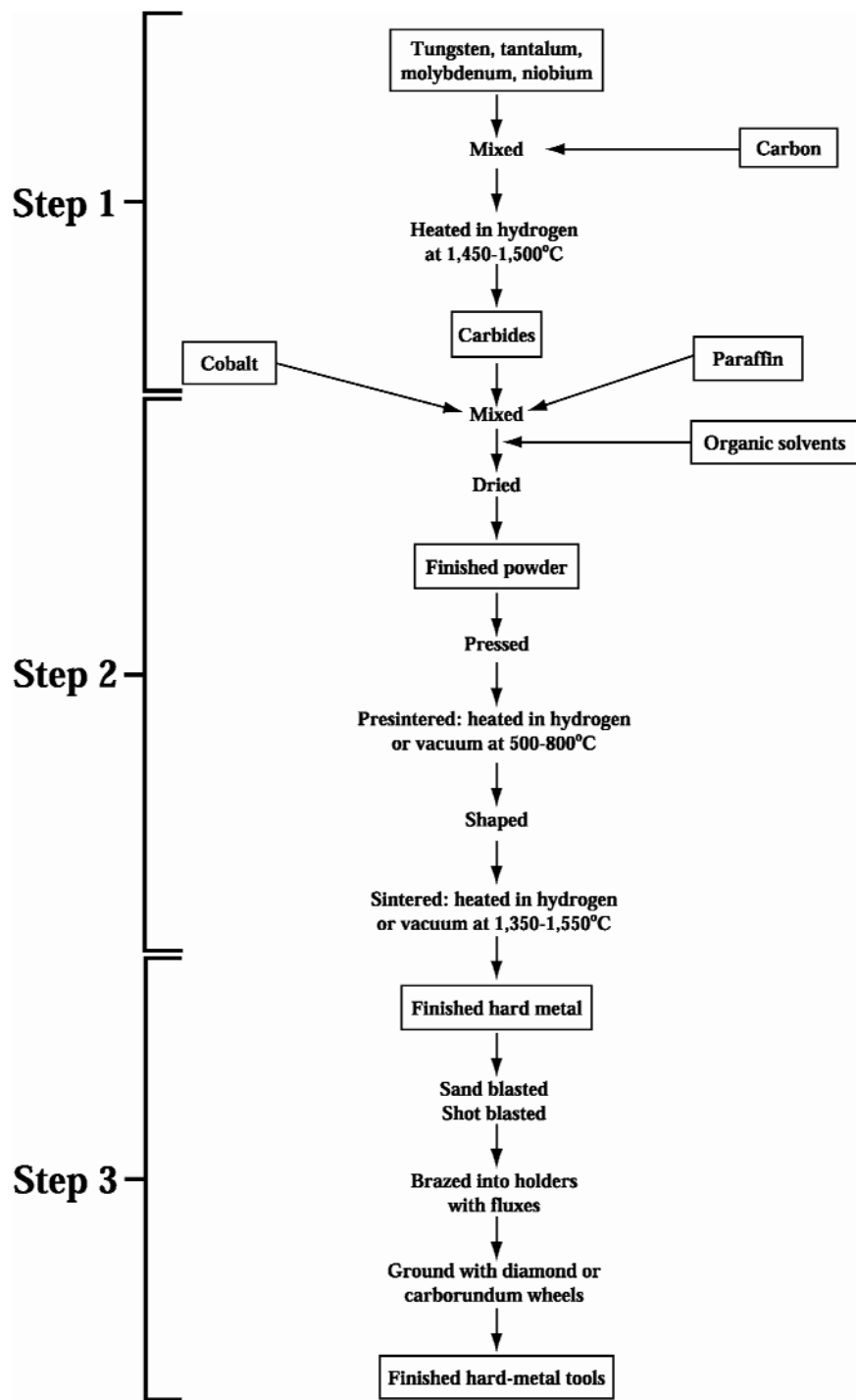
Figure 2-1. Hard-metal manufacturing process

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 2.4.1 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.

1   2.4.2   *Characteristics of hard-metal dusts across the production process*

2   Yamada *et al.* (1987) and Linnainmaa *et al.* (1996) analyzed dusts from different stages

3   and found no difference in particle size or shape. However, Stefaniak *et al.* (2007) noted

4   differences in particle size [and hence respirable fraction], morphology, and

5   concentrations for airborne dusts and bulk dusts from different production areas. Mass

6   median aerodynamic diameter (MMAD) was smallest for grinding operations (2 μm) and

7   largest for scrap reclamation operations (> 18 μm). [Note that scrap reclamation was not

8   part of the operations process for data reported by Yamada *et al.* (1987) and Linnainmaa

9   *et al.* (1996) discussed above.] For cobalt-containing particles, the minimum MMAD was

10   6 μm (dry grinding) and the maximum MMAD was > 18 μm (both for scrap reclamation

11   and pressing operations); the MMAD was around 10 μm for powder mixing. [In general,

12   particles with a diameter of less than 10 μm are considered respirable.]

13   Airborne dust concentrations were highest in mixing operations (4,031 μg/m^3) and lowest

14   in dry-grinding operations (128 μg/m^3) (Stefaniak *et al.* 2007). It was noted that cobalt

15   concentrations in airborne dust varied by a factor of almost 200, with the lowest

16   concentrations in dry grinding (1 μg/m^3), and the highest levels in scrap reclamation (192

17   μg/m^3). The authors pointed out that the particles were predominantly non-respirable in

18   the operations with the highest concentrations.

19   Both Stefaniak *et al.* (2007) and Koponen *et al.* (1982) reported that the morphology of

20   particles changes through the production process. These authors reported that in the

21   mixing stage of the production process, tungsten and cobalt were seen as discrete

22   particles; however, in all subsequent stages of production, heterogeneous, multi-

23   constituent particles consisting of cobalt, tungsten, and various additives were seen, and

24   these particles differed from each other based on the stage of production. Koponen *et al.*

25   reported that grinding of hard-metal pieces generated dusts with similar amounts of

26   tungsten and cobalt compared with dusts generated during the mixing of the raw

27   powders.

1 2.4.3 *Hard-metal recycling*

2 Recycled hard-metal scrap is an important source of tungsten and cobalt for industrial

3 processes, including hard-metal production (USGS 2004), and as noted above, the

4 recycling process is a potential source of significant exposure. The recycling processes

5 that are used can be classified as either direct or indirect. In direct recycling, the hard-

6 metal is disaggregated by processes including the coldstream process and the zinc

7 process, and the finer tungsten-carbide and cobalt powders that result are ready to use to

8 make new hard-metals. The zinc process is considered the most important direct

9 recycling process in the United States for hard-metals recycling (USGS 2005). In indirect

10 processes, the individual components (e.g., tungsten and cobalt) are recovered and

11 purified separately using chemical processes, such as chlorination, nitrate or nitrite-

12 carbonate fusion, and oxidation-sodium hydroxide leaching, with the latter being the

13 most common in the United States (USGS 2004, 2005).

14 In the United States, in the late 1990s it was estimated that 35% of hard-metal scrap was

15 recycled using chemical processes, 25% using the zinc process, and 5% using other

16 methods: the remaining 35% of scrap was not recycled (USGS 2005). Hard-metal

17 producers will often supply scrap to converters for reuse, and some facilities have their

18 own recycling operations. Some of the recycling operations result in high dust levels

19 (Kirk-Othmer 1997), although Stefaniak *et al.* (2007) reported that the respirable fraction

20 of particles from these processes is generally low.

21 2.4.4 *Occupational exposure for various manufacturing processes*

22 The major source of exposure to cobalt–tungsten carbide powders and hard metals is

23 from occupational exposure, which can occur at almost any stage of hard-metal

24 production. [Note that no combined exposure to cobalt and tungsten carbide would be

25 expected to occur in Step 1.] Sources of exposure can include Step 2 processes from the

26 mixing of the cobalt and tungsten carbide powders through sintering, and Step 3

27 processes of grinding and sharpening sintered products (see Figure 2-1). Step 2 processes

28 are generally associated with the highest airborne exposures, with levels up to

29 approximately 7,000 $\mu g/m^3$ for cobalt reported in several studies (see Table 2-3). In

30 comparison, the cobalt levels for the finishing operations in Step 3 did not exceed 1,000

1   μg/m^3 (see Table 2-4). Exposure to cobalt–tungsten carbide hard metals also can occur

2   during processing of hard-metal scrap for recycling and from other miscellaneous

3   operations as well as for operations outside of the direct manufacturing process and

4   during end-use and maintenance of hard-metal tools. [Note that Tables 2-4 and 2-5

5   briefly summarize the data for exposure, and additional data for the same studies are

6   reported in Appendix B, Tables B-1 and B-2.]

7   Occupational exposures reported for Step 2 are discussed in Section 2.4.5, those for Step

8   3 in Section 2.4.6, and exposures that were reported for hard-metal manufacture but were

9   not process specific are reported in Section 2.4.7. The studies by Kraus *et al.* (2001) in

10   Germany and Kumagai *et al.* (1996) in Japan are discussed separately since they reported

11   exposures across a broad range of processes (across Steps 2 and 3), and the levels for the

12   various processes reported in these studies are summarized in Tables 2-2 and 2-3. The

13   highest air level presented by Kraus *et al.* (343 μg/m^3) was based on one personal sample

14   during sintering; however, a level of 1.3 μg/m^3 was reported for one stationary sample

15   during sintering. [This information coupled with the observation of relatively low levels

16   of urinary cobalt for workers involved in sintering and low tungsten air levels during

17   sintering suggests that the high air level based on the single sample might be an

18   anomaly.] Aside from that singular level for sintering, pressing operations and powder

19   processing resulted in the highest air levels for both cobalt and tungsten. Grinding

20   operations resulted in relatively low exposure levels for cobalt, but moderately high

21   levels for tungsten. Kumagai *et al.* similarly found the highest cobalt air levels in powder

22   preparation and press operations, with moderate levels from grinding operations.

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/m³) {N}	Urine (µg/g) {N}	Air (µg/m³) {N}	Urine (µg/g) {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}	NA	3.4 (1.5–5.3) {2}

Source: Kraus *et al.* 2001.
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/m³.
[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 (samples)	Exposure level (µg/m³) Mean (range)
Powder preparation rotation full-time	15 (60) 2 (12)	459 (7–6,390) 147 (26–378)
Press rubber steel	8 (26) 23 (34)	339 (48–2,910) 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.

1   Hard-metal coatings can be applied to the surface of tools by the process of detonation

2   coating, which is generally done in sealed booths. Workers may be contaminated with

3   dusts that did not contact the target parts (overspray). These dusts may be re-aerosolized

4   when workers enter the booth after the coating process (Keane *et al.* 2002). [No data

5   were found on exposure levels from these operations, however.]

6   2.4.5   *Exposure levels associated with Step 2 and other processes*

7   Numerous studies have characterized exposure levels (air and biological) across the

8   various stages of hard-metal production, but the processes in Step 1 (see Figure 2-1) are

9   not expected to involve combined exposures to cobalt and tungsten, although cobalt was

10 reported to be detectable in air at a relatively low level (0.39 $\mu g/m^3$) during production of

11 tungsten carbide in the study by Kraus *et al.* (2001). The exposure data specific to Step 2

12 of the hard-metal production process is described below, and the various studies are

13 summarized in Table 2-3. Information on exposure during reclamation of scrap hard

14 metal and on exposure to non-production personnel at manufacturing plants is also

15 discussed.

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

18 Step 2 involves mixing of the powders, drying, pressing, presintering, shaping of the

19 presintered hard metal, and sintering and generally seems to be associated with the

20 highest airborne exposures to both cobalt and tungsten. For the studies summarized in

21 Table 2-3, the highest levels of cobalt in air were reported from one of the two plants

22 studied by Sprince *et al.* (1984) in the United States during weighing and mixing of

23 powders (mean = 32,740 $\mu g/m^3$; range = 44 to 438,000 $\mu g/m^3$), the same plant also had

24 high concentrations of cobalt in air for milling operations (mean = 8,661 $\mu g/m^3$; range =

25 91 to 48,148 $\mu g/m^3$) followed by pressing (mean = 755 $\mu g/m^3$; range = 13 to 7,359

26 $\mu g/m^3$). For the second plant, the highest levels were also for weighing and mixing of

27 powders (mean = 327 $\mu g/m^3$; range = 20 to 1,480 $\mu g/m^3$) and milling (mean = 282 $\mu g/m^3$;

28 range = 15 to 800 $\mu g/m^3$). Mean levels were also high for pressing (326 $\mu g/m^3$) and

29 drying (337 $\mu g/m^3$).

1   A more recent study of exposures in the United States (Stefaniak *et al.* 2007) reported

2   relatively low levels (ranging from 9 to 145 $\mu g/m^3$) for cobalt in air for powder mixing,

3   spray drying, screening, and pressing, and the authors of this study noted that the levels

4   of airborne cobalt were low relative to historical levels published during the 1980s and

5   1990s. The levels associated with Step 2 processes reported between 1984 and 2007 were

6   highest for pressing or shaping/forming operations (range = 48 to 5,270 $\mu g/m^3$) in studies

7   for companies in Japan (Kumagai *et al.* 1996, Kusaka *et al.*1986b, Kusaka 1996,

8   Ichikawa *et al.* 1985) and Italy (Sala *et al.* 1994).

9   Tungsten air levels were only reported by Kraus *et al.* (2001), Sabbioni *et al.* (1994a),

10 and NIOSH (1977). Kraus reported a maximum value for tungsten (97.4 $\mu g/m^3$) during

11 forming operations with much lower levels for sintering operations (5.9 and 12.9).

12 Sabbioni *et al.* reported a maximum mean tungsten airborne level of 150 $\mu g/m^3$ during

13 weighing operations; however, the maximum mean level of airborne tungsten considered

14 respirable [< 7 μm] was 3.1 $\mu g/m^3$. For powder mixing operations, Sabbioni *et al.*

15 reported a maximum tungsten level of 210 $\mu g/m^3$ (mean = 26 $\mu g/m^3$). A review by

16 NIOSH (1977) reported much higher tungsten air levels for powder processing (880–

17 25,600 $\mu g/m^3$), casting operations (520–17,600 $\mu g/m^3$), and forming operations (80–

18 26,700); however, very limited additional information was provided, and some data were

19 inconsistent within the report. The report noted that the regulatory limit of 6 mg/m^3 was

20 rarely exceeded in these operations; [therefore, the higher levels likely occurred

21 infrequently].

22 *Reclamation (recycling) of hard metals*

23 Two studies in the United States (Sprince *et al.* 1984, Stefaniak *et al.* 2007) reported air

24 concentrations for reclamation of hard-metal scrap. Sprince *et al.* reported a range of 114

25 to 1,708 $\mu g/m^3$ for the two plants that they studied, while Stefaniak *et al.* reported a range

26 of 21 to 192 $\mu g/m^3$ for the reclamation operations including scrap loader, ball mill, and

27 large and small crusher.

1   *Miscellaneous operations*

2   A few papers reported exposure data for jobs outside of the production process.

3   McDermott *et al.* (1971) reported air concentrations of cobalt during packing operations

4   (10 to 250 $\mu g/m^3$), equipment cleaning (40 to 820 $\mu g/m^3$), and miscellaneous operations

5   (10 to 6,700 $\mu g/m^3$), but the nature of these operations was not defined further.

6   Maintenance (including housekeeping) activities were reported by Scansetti *et al.* (1985)

7   to result in exposure greater than 50 $\mu g/m^3$, while Kraus *et al.* (2001) reported urinary

8   levels associated with maintenance of 1.3 to 4.7 $\mu g/L$ for cobalt and 1.5 to 5.3 $\mu g/L$ for

9   tungsten. Pellet *et al.* (1984, as reported by Angerer and Heinrich 1988) reported

10   exposures for a category of "using hard metals" ranging from 180 to 193 $\mu g/m^3$ for air

11   and a mean of 11.7 $\mu g/L$ for urine.

Table 2-3. Hard-metal exposure levels from manufacturing operations (levels are for cobalt unless otherwise noted)

Stage of the hard-metal production process	Air concentration[a] mean (range) µg/m³ {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 Highest respirable mass percentage for powder mixing; lowest for scrap reclamation	Stefaniak *et al.* 2007 (USA, NR)
Powder processing, forming, pressing, sintering, maintenance	*Cobalt* NR (0.61–343) {15} *Tungsten* NR (5.3–254) {15}	*Cobalt* 4.1–28.5 {75} *Tungsten* 3.4–12.5 {75}	Highest mean Co air level for sintering; lowest for forming Highest mean W air level for powder processing; lowest for pressing Highest urinary Co level for powder processing (227.8 µg/dL); lowest for sintering (0.31 µg/dL) Highest urinary W level for pressing (71.0 µg/dL); lowest for forming (0.33 µg/dL)	Kraus *et al.* 2001 (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 (Japan, NR)
Shaping, sintering	25 & 141 (7–436) (27)	Urine: 1 & 2 {NR} Blood (µg/dL): 0.28 & 0.42 {NR} Hair (ppm): 25.8 (shaping) {NR}	Higher Co air and blood levels from shaping	Kusaka 1996 (Japan, NR)

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

Stage of the hard-metal production process	Air concentration[a] mean (range) $\mu g/m^3$ {N}	Biological levels[a] mean (range) $\mu g/L$ {N}	Additional information	Reference (Location, year of measurement)
Pressing, forming, sintering, finishing (testing), maintenance	< 10 to > 100 {NR}	Monday: up to 36 {26} Friday: up to 63 {26}	Highest levels for hand pressing; lowest for sintering	Scansetti *et al.* 1985 (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 Sampling conducted in a manner to obtain peak levels	Sprince *et al.* 1984 (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 (NR, NR)
Powder mixing, pressing, general maintenance	25–48 (NR) {NR}	NA	Highest levels for powder mixing; lowest for general maintenance	NIOSH 1981 (USA, 1977–8)
Powder processing, tool & die operations, casting, forming	*Cobalt* 0–6,800 {NR} *Tungsten* 80–26,700 {NR}	NA	Highest Co air levels for casting; lowest for both powder processing and casting Highest & lowest W air levels both reported for forming	NIOSH 1977 (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 $\mu g/m^3$) reported for metal preparation, press operations, surface grinding, and drilling operations	McDermott 1971 (USA, NR)

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

1   2.4.6   *Exposure during finishing of sintered hard-metal products*

2   The final step in hard-metal manufacturing consists of various finishing operations as

3   illustrated in Step 3 of Figure 2-1, and this section discusses occupational exposure

4   associated with those processes. Important exposure determinants with exposure levels

5   presented in Table 2-4 are discussed first, followed by engineering controls to reduce

6   exposures, and the findings on the respirable fractions for cobalt and tungsten in dust.

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

8   Post-sintered products are often finish-ground or sharpened at the production facility to

9   specified dimensions or characteristics. Hard-metal products also may require

10   maintenance and sharpening after use. In fact, in 1995 the Washington State Department

11   of Labor and Industries warned that workers who file saw blades and those who machine

12   tools made of hard metal may be exposed to toxic levels of cobalt (WSDLI 1995). This

13   section discusses exposures that occur both from finish operations at the production

14   facility, and from grinding and resharpening operations after use. [Since both procedures

15   involve grinding or sharpening of post-sintered products, there should be no appreciable

16   difference in the chemical or physical properties between the dusts generated.] These

17   exposures may occur at facilities that produce both the cobalt–tungsten carbide hard

18   metal and the end-use hard-metal products, at small businesses that recondition dull or

19   broken hard-metal tools, or in tool reconditioning or machining shops within larger

20   businesses that use hard-metal tools (for example, lumber mills often employ full-time

21   saw sharpeners).

22   Sesana *et al.* (1994) noted that the assessment of exposure from grinding hard-metal tools

23   has not received satisfactory attention from industrial hygienists, probably because the

24   industry consists of small facilities that usually employ relatively few workers (generally

25   fewer than 10 workers). Exposure circumstances may vary for the same job type based on

26   the size of a company. In small workshops that mainly perform sharpening operations,

27   grinders will often be exposed for 6 to 8 hours per day, while in large metallurgical and

28   mechanical industries where operations are carried out in tool or machine shops,

29   exposure generally will range from 30 minutes to 3 or 4 hours per day (Imbrogno and

30   Alborghetti 1994). Exposure from this industrial segment has the potential to be

1   extensive. Although data from the U.S. Economic Census and the Annual Survey of

2   Manufacturers indicated that in 2002 there were 3,461 sawmills in the United States,

3   employing 95,452 workers (USDC 2005), no breakdown of these data was provided to

4   identify how many of these workers were employed in tool-maintenance or grinding

5   operations that could result in exposure to cobalt–tungsten carbide. However, sawmills

6   are only one segment of the industries that perform sharpening and grinding operations

7   on hard-metal products.

8   The operations that are discussed in this section include primarily grinding and

9   sharpening operations, including both wet-grinding and dry-grinding processes. Other

10   hard-metal finishing processes include blasting and electron discharging (Kumagai *et al.*

11   1996, Kusaka *et al.* 1986b) (see Table 2-2); however, these processes result in cobalt air

12   concentrations that are one to four orders of magnitude less than grinding operations.

13   Kraus *et al.* (2001) reported higher levels from dry grinding when compared with wet

14   grinding. (See below for a further discussion of exposure issues associated with wet-

15   grinding.) In Table 2-4, if the study authors reported the type of grinding process that was

16   used, that information is included, [but most studies did not specify the grinding process

17   used].

18   Table 2-4 also provides some information on total dust levels from grinding operations

19   and associated levels of cobalt (Koponen *et al.* 1982, Linnainmaa *et al.* 1996, Posma and

20   Dijstelberger 1985, Stefaniak *et al.* 2007) and tungsten (Koponen *et al.* 1982). Cobalt

21   levels generally were less than 10% of the total dust (Stefaniak *et al.* 2007, Linnainmaa *et*

22   *al.* 1996, Posma and Dijstelberger 1985, Koponen *et al.* 1982); although Posma and

23   Dijstelberger reported the upper end of the range to be 17%. Koponen *et al.* (1982)

24   reported that tungsten levels in dust ranged from 66% to 73%.

25   The biological monitoring data that are presented in Table 2-4 consist primarily of cobalt

26   levels in urine; however, data also were reported for tungsten in urine (Goldoni *et al.*

27   2004, Kraus *et al.* 2001, Sabbioni *et al.* 1994a, Della Torre *et al.* 1990) and/or cobalt in

28   blood (Della Torre *et al.* 1990, Ichikawa *et al.* 1985, Kusaka 1996, Sabbioni *et al.* 1994a),

29   hair (Kusaka 1996, Sabbioni *et al.* 1994a) and toenails (Sabbioni *et al.* 1994a) (see

1   Appendix B, Table B-2). Biological data presented in Table 2-4 generally show higher

2   levels in exposed subjects versus unexposed controls (Goldoni *et al.* 2004, Ichikawa *et al.*

3   1985, Posma and Dijstelberger 1985), in levels assessed later in the week when compared

4   with earlier in the week (Sesana *et al.* 1994), and in post-shift levels when compared with

5   pre-shift levels (NIOSH 1987a, 1987b); however, these differences were usually reflected

6   in higher associated air levels that were measured in concert with the biological levels.

7   (See Section 2.3 for a more detailed discussion of biological indices of exposure.)

8   Higher exposure levels have been seen in wet-grinding operations compared with dry-

9   grinding operations in some studies (Imbrogno and Alborghetti 1994, Stebbins *et al.*

10   1992), but wide variations in cobalt levels in hard-metal wet-grinding metal-working

11   fluids have been reported, [and no data were found on tungsten levels in metal-working

12   fluids] (Kennedy *et al.* 1995, NIOSH 1987a, 1987b, Stebbins *et al.* 1992, Teschke *et al.*

13   1995). Cobalt in hard-metal wet-grinding metal-working fluids has been shown to exist

14   as both carbide particles suspended in the metal-working fluids and as dissolved cobalt

15   (Stebbins *et al.* 1992).

16   *Engineering controls to limit exposure*

17   Several studies have assessed the effects of engineering controls, in particular air

18   ventilation controls, on airborne cobalt levels. A number of studies have reported levels

19   that exceeded regulatory limits or NIOSH guidelines before the installation of ventilation

20   systems, with reductions to levels below the regulatory or guideline limits after

21   ventilation systems were installed (Lichtenstein *et al.* 1975, Paulsen and Kilens 1994,

22   Sala *et al.* 1994, Simcox *et al.* 2000). However, levels exceeding regulatory limits were

23   measured even after controls were installed in the study by Sala *et al.* (1994). Although

24   drastic reductions of cobalt exposure levels were seen after the installation of ventilation

25   systems, Simcox *et al.* (2000) nonetheless concluded that airflow associated with the

26   ventilation systems alone did not guarantee low exposures, and that proper hood design

27   and worker acceptance and proper use of the hoods were important factors impacting

28   exposure levels.

1   *Respirable mass*

2   Only a portion of the total air levels of dust or cobalt from finishing operations represent

3   respirable mass (Kusaka *et al.* 1992, Linnainmaa *et al.* 1996, NIOSH 1987a, 1988,

4   Sabbioni *et al.* 1994a, Stebbins *et al.* 1992, Stefaniak *et al.* 2007). The percentage of

5   respirable mass for cobalt and tungsten varied widely even between methods that

6   reported the same particle-size cutoff value. Kusaka *et al.* (1992) and Sabbioni *et al.*

7   (1994a) both used a particle-size cutoff of < 7 μm, but Kusaka *et al.* reported that cobalt

8   in the respirable fraction was 70.1% of that in total dust for air samples from a hard-metal

9   grinding worksite, while Sabbioni *et al.* reported that dry-grinding operations in their

10   study had cobalt in the < 7 μm fraction that ranged from 3.7% to 11.3%. Intermediate

11   values (ranging between approximately 13% and 30%) were reported by Stebbins *et al.*

12   (1992), NIOSH (1988), and NIOSH (1987a), but the cutoff value was not specifically

13   defined in these studies.

14   2.4.7   *Exposure to end-users (other than grinders or sharpeners)*

15   Pellet *et al.* (1984, as cited in Angerer and Henirich 1988) reported a range of 180 to 193

16   μg/m^3 cobalt air levels and a mean urinary cobalt level of 11.7 μg/L associated with using

17   hard metal; however, no additional information was provided for these data. No other

18   information was located that directly demonstrated exposure to cobalt–tungsten carbide

19   powders and hard metals for end-users of products containing the material. The

20   Washington State Department of Labor, in a Hazard Alert issued in March 1995, stated

21   that there was no evidence of substantial exposure to cobalt during the use of tools

22   containing tungsten carbide or other hard metals (WSDLI 1995). Alcaraz (2004) assessed

23   occupational exposure to hard-metal particulates for 11 different shops in the state of

24   Washington that were characterized as either saw manufacturers, saw repair shops, or

25   saw mills. This study showed that saw mills had the lowest exposures of the three types

26   of operations assessed, supporting the assertion that end-use is expected to result in less

27   exposure than either manufacturing or maintaining the hard-metal products.

Table 2-4. Hard-metal exposure levels from grinding and sharpening operations (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 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	Simcox *et al.* 2000 (USA, 1995)
Grinding hard-metal and stellite	NR ({1–70}) {91}	14.2 (0.5–160) {131}	Measurements from 16 workplaces.; air range estimated from graph	Linnainmaa and Kiilunen 1997 (Finland, NR)
Tool manufacturing and blade repair	17[f] (2–240) {87}	NA	Includes data for grinding of stellite	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)
Grinding	31 & 36 (2–40) {13}	Urine: 9 & 29 {2} Blood: 0.32 & 0.4 ($\mu g/dL$) {2}	Data are for two grinders	Kusaka 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)
		Hair: 3.42 & 9.11 (ppm) {2}		
Grinding hard-metal blades	A: NR (1–160) {87} B: NR (< 2–28) {43}	A: NR (6.1–63) {26}[g] B: NR (0.4–62) {20}[g]	"A" = levels before ventilation installed, "B" = levels after ventilation installed	Linnainmaa 1995 (Finland, NR)
Grinding hard-metal and stellite saws	9 (< 0.64–106) {278}	NA	Data are from personal sampling for 112 workers	Teschke et al. 1995 (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 (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 (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 (Italy, NR)
Wet grinding (3 factories)	6.4–376[f] (NR) {60}	15.3–138.3[f] (NR)	Mean level at facility with maximum level fell to 9.9 μg/m^3 after ventilation installed	Sesana et al. 1994 (Italy, NR)
Hard-metal tool grinding	w/o: 91[f] & 40[f] (5.0–1,338) {103} w: 9[f] & 12[f] (1.0–58) {102}	NA	"w/o"= plants without ventilation system. "w"= plants with ventilation system	Sala et al. 1994 (Italy, NR)
Sharpening operations	10[f] (4–70) {15}	NA	Noted as before ventilation control installed; no data provided for after	Sala et al. 1994 (Italy, NR)
Grinding and sharpening	NA	17 nmol/mmol CR {~150}	19 nmol/mmol CR presented for hard-metal manufacturing which included pre-sintering operations and post-sintering grinding	White and Dyne 1994 (U.K., NR)
Hard-metal tool grinding facilities	w/o: 6.68[f] & 47.75[f] (NR) {34} w: 3.47[f] & 4.43[f] (NR) {23}	WO: 28.5[f] ± 3.97[h] {6} W: 2.66[f] ± 1.69[h] {8}	"w/o"= plants without aspirators "w"= plants with aspirators	Cereda et al. 1994 (Italy, NR)
Grinding (across 2	Cobalt	CoB 45.6 (1–245) {88}	< 7 μm is the concentration in the air	Sabbioni et al.

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)
factories)	64–985 (NR) {NR} < 7 µm: 4–14 (NR) {NR} *Tungsten* 2.1–77 (NR) {NR} < 7 µm: 0.13–2.4 (NR) {NR}	CoU 303.6 (0.75–5,500) {88} CoH 49.1 (110–910,000)[i] {90} CoN 53.792 (109–580,000)[i]{92} WB 1.2 (0.04–6.5) {43} WU 6.7 (0.11–230) {78} WH 2,147 (25–59,000)[i]{75} WN 3,056 (27–105,000)[i]{82}	fraction measuring less than 7 microns {considered respirable} measured by stationary sampling. Biological data were aggregated and summarized across all workers irrespective of production stage or factory	1994a (Bergamo Province, Italy, NR)
Grinding operations	11–87.4 (NR) {37}	12.2 & 33.6 (2.6–38) {19}	Levels across 3 datasets. High urinary level for wet grinding, low level for dry grinding	Stebbins *et al.* 1992 (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 (Japan, NR)
Sharpening and grinding operations	NA	Urine: [14.17] (2.5–35) {6} Blood: [4.0] (1.5–9) {6} *Tungsten* Urine: [192] (2–1,000) {6} 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 (Italy, NR)
Grinding, sharpening, and tooling	Respirable: 4 (ND–4) {31} Total: 30.2 (ND–97) {33}	NR (ND–7.6) (63)	Only thirty percent of urine samples exceeded detection limit	NIOSH 1988 (USA, NR)
Saw blade and tool sharpening	[9.38–45] (2.8–63) {7} *Tungsten* [186 & 645] (ND–925 {6}	2.74–18.3 (ND–23.8) {48} *Tungsten* NA	Data across several groups of workers. Minimum cobalt level from an office worker control group	NIOSH 1987b (USA, NR)
Finish grinding of hard-metal	*Cobalt* Respirable: [4.3] (ND–8.4) {24} Total: 13.5 (ND–26.8) {24} *Tungsten* 280 (ND–410) {24}	*Pre-shift* 10.5 (4.7–19)[d] {10} *Post-shift* 18.09 (8.4–27.7)[d] {10}	Respirable airborne cobalt was significantly associated with post-shift urinary cobalt levels (P = 0.003) {Tungsten in air assumed to be total level}	NIOSH 1987a (United States, NR)

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)
Blasting, electron discharging, grinding	3–1,292 (1–1,471) {217}	NA	Wet grinding mean was 53 $\mu g/m^3$, dry grinding mean was 1,292 $\mu g/m^3$	Kusaka *et al.* 1986b (Japan, 1981–1984)
Wet-grinding	44–317 (3–1,203) {107}	Urine: 17–68 (1–265) {107} Blood: 3.3–6.5 (1–39) {107}	Maximum air and blood urine for workers who used respirators	Ichikawa *et al.* 1985 (Japan, NR)
Grinding operations	Dust: 4.3 (0.3–15) mg/m³ {NR} 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 (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 (USA, NR)
Grinding operations in a hard-metal plant	*Dust* 2,100 (1,500–3,000) {4} *Cobalt* 7%–9% of dust concentration *Tungsten* 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 (Finland, NR)
Grinding operations	19 (NR) {NR}	NA	No additional information provided	NIOSH 1981 (NR, 1977–1978)
Dry grinding without exhaust	NR (40–2,440) {NR}	NA	No additional information provided	NIOSH 1977 (Switzerland, NR)
Wet grinding	240 & 280 (30–930) {37} *Tungsten* 3,930 & 5,160 (< 200–12,800) {37}	NA	Two sets of data based on personal or stationary sampling	Lichtenstein *et al.* 1975 (United States, NR)

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

[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] Geometric mean.

[g] 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.

[h] Geometric standard deviation.

[i] ng/g

1   2.4.8   *Non-process–specific exposure data for hard-metal production*

2   Several studies presented occupational exposure data for hard-metal production without

3   providing detail regarding the production stage where the exposure took place (Angerer

4   and Heinrich 1988, Gallorini *et al.* 1994, Lison *et al.* 1994, NIEHS 2002, Sabbioni *et al.*

5   1994a, Sala *et al.* 1994, Scansetti *et al.* 1998, Torra *et al.* 2005). Table 2-5 presents these

6   non-process–specific occupational exposure data for hard-metal production.

7   Urinary cobalt levels for hard-metal workers have been seen to increase through the

8   workday (Torra *et al.* 2005) and workweek (Torra *et al.* 2005, Scansetti *et al.* 1998, Lison

9   *et al.* 1994). Torra *et al.* (2005) reported that urinary cobalt concentrations were

10   significantly higher ($P < 0.005$) at the end of a shift than at the beginning of the shift with

11   significant increases "day in and day out" during the workweek. In all cases, workplace

12   air concentrations were higher than the ACGIH Threshold Limit Value (TLV) of 20

13   $\mu g/m^3$, and the authors reported that 85% of the workers analyzed had urinary cobalt

14   levels that exceeded the ACGIH BEI level of 15 $\mu g/L$.

15   Sala *et al.* (1994) assessed air level reductions due to the installation of ventilation. The

16   authors noted that substantial air level reductions were seen across all stages of the hard-

17   metal manufacturing process with significant reductions seen in grinding operations (see

18   Section 2.5.3).

19   Among a group of patients occupationally exposed to hard metals who presented with

20   asthma and/or fibrosis, Sabbioni *et al.* (1994a) reported cobalt levels in bronchoalveolar

21   lavage (BAL) ranging from less than 0.7 to 10.1 $\mu g/L$ (12 patients) and 0.2 to 7 $\mu g/L$ for

22   tungsten (10 patients). Open lung biopsy was performed on two patients with wet-weight

23   levels of 830 and 2,440 ng/g for cobalt, and 52,000 and 107,000 ng/g for tungsten.

24   Transbronchial biopsy was performed on 5 patients with wet-weight levels ranging from

25   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} ($\mu g/m^3$)	Concentration in biological samples[a] Mean (range) {N} ($\mu g/L$)	Reference (Location)
Hard-metal manufacture (NR)	100 (79–130) {3}	*Worker urine* 46 (11–110) µg/g CR {19} *Unexposed control urine* 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} Thu: 31.66 (7–92) {6}	*Urine* 13.23 (2.58–29.8) {6} 30.87 (8.17–62.6) {6}	Scansetti *et al.* 1998 (Italy)
Hard-metal tool production (mixing, sintering, grinding) (NR)	NA	CoU: 13.9 (1.2–309) {24} CoB: 5.06 (0.7–12.5) {20} CoH: 9,607 (1,050–29,900)[b] {22} CoN: 18,904 (2,000–109,000)[b] {23} WU: 9.32 (1.1–25.5) {21} WB: 1.29 (0.11–10) {16} WH: 7,018 (227–76,000)[b] {20} 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} CoH: 13,390 (805–13,600)[b] {28} WU: 12.8 (0.35–55) {24} WH: 9,585 (340–40,000)[b] {24}	Sabbioni *et al.* 1994a (Turin, Italy)
Hard-metal manufacture (NR)	Mon.: 9[c] (2–127) {10} Fri.: 19[c] (1–203) {10}	*Urine* 13.1[c] (3.1–87.5) µg/g CR {10} 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)* 189–1,254 (NR) {20} *Unexposed controls urine* 0.85 (NR) {5}	Gallorini *et al.* 1994 (Italy)
Hard-metal workers, ranges from 3 studies (NR)	(NR) 9–13,600 {NR} (NR) 10–60 {NR} (NR) 1–11,000 {NR}	NA	NIEHS 2002 (NR)
Medium-sized hard-metal plant before and after ventilation	*Before* 428 (139–978) {21} *After* 14 (6–40) {7}	NA	Sala *et al.* 1994 (Italy)
Hard-metal-producing industry (2 subgroups) (NR)	(a) 90 (NR) {NR} (b) 10 (NR) {NR}	*Blood* (a) 10.5 (NR) {NR} (b) 0.7 (NR) {NR} *Urine* (a) 134 (NR) {NR} (b) ~ 3 (NR) {NR}	Alexandersson and Lidums 1979 as cited in Angerer and Heinrich 1988 (Russia)

N = number of samples, NA = not assessed, CoB = cobalt in blood, CoN = cobalt in toenails, CoH = cobalt in hair, CoU = cobalt in urine, CR = creatinine, 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.

1   **2.5   Environmental levels and general population exposure**

2   The potential exists for exposure of people who live in the vicinity of hard-metal

3   production or maintenance facilities to cobalt–tungsten carbide hard-metal dusts. While

4   no exposure levels for the general public were found, this section describes studies that

5   provide data for possible environmental contamination from the manufacture or

6   maintenance of hard-metal products. In addition to the studies discussed below, a Finnish

7   study of tungsten carbide in urban street dust resulting from the use of tires with hard-

8   metal studs, reported tungsten levels ranging from 9.2 to 39 μg/g depending on the

9   particle size fraction of the dust (Peltola and Wikstrom 2006).

10   Abraham and Hunt (1995) investigated environmental contamination in the vicinity of a

11   cemented tungsten carbide tool-grinding plant. At this facility, waste dusts generated

12   from the grinding operation were swept from inside the building, out the backdoor, to

13   open ground at the rear of the plant, [but the use of air pollution control devices was not

14   discussed]. Ventilation fans from inside the facility emitted dust to the outside air. Soil

15   sampled from the rear of the factory contained cobalt levels as high as 12,780 mg/kg.

16   Cobalt levels at the plot that had been used by local residents for gardening 20 m behind

17   the building were 100 mg/kg in a cultivated area and 1,800 mg/kg in an uncultivated area.

18   Concentrations ranged from 12 to 18 mg/kg in samples taken at 30 to 160 m from the

19   building. The highest cobalt levels were over 1,700 times higher than the average value

20   for cobalt in the soil in the United States, which the authors noted as 7.2 mg/kg. X-ray

21   micro-analysis examination of the waste dust particles revealed that the individual

22   particles were composites containing both cobalt and tungsten. The authors noted that

23   studies had not been conducted on the local residents to assess exposure and that the

24   scope of similar industrial/environmental contamination is not known.

25   A series of publications (Sheppard *et al.* 2006a, b, c, 2007a, b, c, d) reported elevated

26   airborne tungsten and cobalt levels in Fallon, Nevada, where a hard-metal manufacturing

1   facility is located. [See Appendix A for a description of a childhood-leukemia cluster that

2   was identified in this area and prompted this and a number of other environmental

3   investigations]. Airborne particulate samples collected by 10 portable, high-volume

4   particulate air samplers at two different times of the year (March to April and November)

5   in Fallon and four nearby towns for comparison purposes (Sheppard *et al.* 2006a,b,c)

6   contained tungsten and cobalt (but not 17 other elements measured) air concentrations

7   that they described as consistently and significantly ($P = 0.001$ to 0.002) higher in Fallon

8   (tungsten = 0.1 to 40.9 ng/m^3; cobalt = 0.04 to 7.5 ng/m^3) than in the surrounding towns

9   (tungsten = 0.02 to 0.16 ng/m^3; cobalt = 0.04 to 0.58 ng/m^3), which modeling studies

10   suggested was not from natural sources. In follow-up studies, Sheppard *et al.* (2006d,

11   2007c) reported higher concentrations of tungsten (12.5 times higher, $P < 0.001$) and

12   cobalt (2.0 times higher, $P = 0.06$) in lichens (which the authors described as serving as a

13   biomonitor for atmospheric chemical composition), but not in the rock substrates of the

14   lichens from Fallon compared with four non-developed desert lands outside of Fallon,

15   and they collected information on the spatial pattern of cobalt and tungsten in the surface

16   dust, which peaked at 98 ppm for cobalt and 934 ppm for tungsten at a location in the

17   vicinity of the hard-metals manufacturing facility located in Fallon. They also examined

18   the temporal variability of cobalt and tungsten in the environment around Fallon through

19   dendrochemistry (the study of elemental concentrations through time in tree rings). For

20   Fallon, the authors reported that for the time period from 1989 to 1992, before the onset

21   of the leukemia cases, median tree-ring tungsten levels were not statistically significantly

22   different from the comparison towns; however, during the time period that centered on

23   1995 (the period right before the onset of the cluster), Fallon tree-ring tungsten levels

24   started trending upward and were statistically higher than levels seen in the comparison

25   towns (Sheppard et al. 2007a, 2008). During the following time periods (through 2002),

26   the tungsten levels in Fallon continued trending upward and remained higher than

27   comparison towns with significance levels at or near $P = 0.05$. The authors noted that

28   cobalt levels in Fallon tree rings were consistently higher than comparison towns

29   (statistically significant for the second and fourth of the four time periods; $P < 0.01$ or

30   0.02), but there was no significant increase through time within Fallon.Some of Sheppard

31   and co-workers' conclusions have been questioned by other investigators, including

1   Seiler *et al.* (2006), Sueker *et al.* (2006), and Schell and Pardus (2008). The issues

2   discussed in these studies are described in more detail in Appendix A.

3   **2.6   Regulations and guidelines**

4   While only one Federal regulation and one guideline have been developed specifically for

5   cemented tungsten carbide [hard metal], numerous regulations and guidelines have been

6   developed for cobalt and tungsten metals and compounds. These regulations and

7   guidelines are presented in Sections 2.7.1 and 2.7.2.

8   2.6.1   *Regulations*

9   **U.S. Environmental Protection Agency**

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

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

12   requirements

13   *Clean Water Act*

14   Effluent Guidelines:

15   Tungsten and cobalt discharge limits are imposed for numerous processes during the

16   production of tungsten or cobalt at secondary tungsten and cobalt facilities processing

17   tungsten or tungsten carbide scrap raw materials

18   Discharge limits for tungsten are imposed for numerous processes during the production

19   of tungsten at primary tungsten facilities

20   Discharge limits for cobalt are imposed for numerous processes during the production of

21   cobalt at primary cobalt facilities

22   **Occupational Safety and Health Administration**

23   Permissible Exposure Limit (PEL) for cemented tungsten carbide containing > 2% Co =

24   0.1 mg Co/m^3 (8-hour TWA)

25   PEL for cobalt metal, dust, and fume (as Co) = 0.1 mg/m^3

26   PEL for insoluble tungsten compounds (as W) = 5 mg/m^3

27   PEL for soluble tungsten compounds (as W) = 1 mg/m^3

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

29   STEL for soluble tungsten compounds (as W) = 3 mg/m^3

1   2.6.2   *Guidelines*

2   **American Conference of Governmental Industrial Hygienists**

3   Threshold Limit Value–Time-Weighted Average (TLV-TWA) limit for cobalt and

4   inorganic cobalt compounds = 0.02 mg/m^3

5   TLV-TWA for tungsten metal and insoluble compounds = 5 mg/m^3

6   Threshold Limit Value–Short-Term Exposure Limit (TLV-STEL) for tungsten metal and

7   insoluble compounds = 10 mg/m^3

8   TLV-STEL for soluble tungsten compounds = 3 mg/m^3

9   Biological Exposure Index (BEI)–cobalt in urine = 15 μg/L end of shift at end of

10   workweek

11   BEI–cobalt in blood = 1 μg/L end of shift at end of workweek

12   **National Institute for Occupational Safety and Health**

13   Recommended exposure limit (REL) (10-hour TWA) for cemented tungsten carbide

14   containing > 2% Co = 0.05 mg Co/m^3

15   REL for cobalt metal dust and fume (as Co) = 0.05 mg/m^3

16   Immediately dangerous to life and health (IDLH) level for cobalt metal dust and fume (as

17   Co) = 20 mg/m^3

18   REL for tungsten and insoluble tungsten compounds (as W) = 5 mg/m^3

19   Short-Term Exposure Limit (STEL) for tungsten and insoluble tungsten compounds (as

20   W) = 10 mg/m^3

21   REL soluble tungsten compounds (as W) = 1 mg/m^3

22   STEL soluble tungsten compounds (as W) = 3 mg/m^3

23   **2.7   Summary**

24   Cobalt–tungsten carbide hard metal is used primarily in cutting tools, to machine

25   tempered steel, in rock drilling bits, and in a variety of tools. It is produced by preparing

26   tungsten carbide from tungsten metal or tungsten oxide and carbon, adding a mixture of

27   powdered cobalt metal and other compounds to produce cobalt–tungsten carbide

28   powders, which are then pressed, shaped, sintered, and finished as hard-metal products.

29   Total U.S. domestic production of hard-metal products was estimated at 5,527 metric

30   tons [6,080 tons] in 2004, and the USGS estimated that 6,610 metric tons [7,286 tons] of

1   tungsten and 792 metric tons [873 tons] of cobalt were used in the production of

2   cemented carbides in the United States in 2007. Workers potentially are exposed to

3   respirable dusts at many points during the manufacturing process. Exposure can be

4   assessed by measuring ambient air concentrations of cobalt or tungsten or by biological

5   monitoring, including measurements of cobalt or tungsten in urine, blood, tissues, or

6   exhaled air. Exposure generally is highest among workers handling hard metal in powder

7   form before or during the sintering process (Step 2). Exposure can also occur during the

8   grinding or sharpening of hard-metal blades (Step 3) and from other processes.

9   Historically, exposure levels from production have decreased over time, possibly as a

10   result of improved industrial hygiene in hard-metal producing factories. The potential

11   exists for general-population exposures to cobalt–tungsten carbide hard-metal powders

12   for persons living near facilities that manufacture or process hard metal or hard-metal

13   products. There is one OSHA regulation specific to cemented tungsten carbide (a

14   synonym for hard metals), although there are numerous other regulations for cobalt and

15   tungsten metals and compounds. Similarly, there is one guideline for cemented tungsten

16   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 2004, 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 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.

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. Elevated levels of airborne cobalt and tungsten were reported but no adequate epidemiological studies have been conducted that evaluated the relationship between childhood leukemia and exposure to cobalt–tungsten carbide hard metals and powders.

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 cobalt–tungsten carbide powders and hard metals primarily occurs in hard-metal producing factories or factories in which hard-metal tools are finished or sharpened by grinding.

1   There are three main steps in the industrial process used in the manufacture of hard-metal

2   tools (see also Section 2.2.1 and Figure 2-1):

3   **Step 1**   the production of the cobalt and tungsten carbide powders;

4   **Step 2**   the mixing of the powders, drying, pressing, presintering, shaping of the

5   presintered hard metal, and sintering; and

6   **Step 3**   the finishing of the sintered products.

7   Depending on the industrial site, all three steps or any of these steps are concomitant, but

8   only the last two steps always give rise to "hard-metal exposures." In the first step,

9   workers may be exposed to only cobalt dust or to only tungsten carbide dust.

10   The primary tissue site relevant to potential carcinogenicity of exposure to cobalt–

11   tungsten carbide powders and hard metals is the lung, through inhalation exposure to

12   hard-metal dust. The leading cause of lung cancer is smoking; however, a number of

13   known or suspected carcinogens (such as polycyclic aromatic hydrocarbons (PAHs),

14   nitroamines [nitrosamines], nickel and chromium and their compounds, arsenic,

15   cadmium, and crystalline silica (quartz)) can be present at the workplace, the most

16   common in the past being asbestos.

17   **3.2   Cohort studies**

18   This section discusses four cohort studies of cobalt–tungsten carbide hard-metal

19   manufacturing workers.

20   3.2.1   *Hogstedt and Alexandersson (1990)*

21   *Population and follow-up*

22   Hogstedt and Alexandersson (1990) studied the workforce (N = 3,163) of three hard-

23   metal producing factories. Factory A (1,191 workers) was established in Stockholm

24   (which had high lung cancer rates) in the 1930s, whereas Factory B (1,869 workers) was

25   established in a rural area in the early 1950s, and Factory C (103 subjects) was

26   established in the 1940s. Mortality was followed from 1951 to 1982; workers who

27   reached age 80 were excluded from further follow-up because the national statistics

28   ended at 80 years of age. Foreign-born workers and those who emigrated from Sweden

29   were excluded. Vital status and death certificates were obtained from the Swedish central

1 statistical office, and causes of death were coded according to *International*

2 *Classification of Diseases, Revision 8* (ICD-8). Expected numbers of deaths by cause

3 were based on national death rates, and Standardized Mortality Ratios (SMRs) were

4 calculated using standard life-table methods.

5 *Exposure assessment*

6 Exposure was assessed retrospectively using measurements from the 1950s and from the

7 1970s, and expert knowledge of working conditions. Workers were classified into the

8 following exposure groups: group 0, unexposed; group 1, intermittent exposure in hard-

9 metal producing workshops; group 2, continuous exposure in hard-metal producing

10 workshops, but without direct involvement in production; group 3, production of hard-

11 metal tools; and group 4, hard-metal production with exposure to powdered cobalt. The

12 specific steps in hard-metal production performed by workers in each group were not

13 described; however, it appears that workers in group 3 were exposed to dust from

14 sintered hard-metal tools (Step 3), whereas workers in group 4 were exposed to

15 unsintered hard-metal dust (Step 2). For statistical analysis, groups 1 and 2 were

16 combined into a low-exposure group, and groups 3 and 4 into a high-exposure group.

17 Each worker's duration of exposure was computed. For the 9 workers assigned to more

18 than one exposure group, the duration of exposure in the highest-exposure group was

19 used. No workers in Factory B were assigned to group 4, and almost all workers in group

20 4 were from Factory A. Based on retrospective estimation, eight-hour cobalt exposure in

21 groups 1 and 2 was always below 5 $\mu g/m^3$; exposure in group 3 ranged from 20 to 30

22 $\mu g/m^3$ from 1940 to 1960 and 10 to 20 $\mu g/m^3$ since 1960; and exposure in group 4 ranged

23 from 500 to 11,000 $\mu g/m^3$ in the 1940s, 60 to 600 $\mu g/m^3$ in the 1950s, 60 to 400 $\mu g/m^3$ in

24 the 1960s, and 60 to 140 $\mu g/m^3$ in the 1970s.

25 *Results*

26 Overall, nonsignificant excesses were observed for lung cancer (SMR = 1.34, 95%

27 confidence interval [CI] = 0.77 to 2.13, 17 deaths), pancreatic cancer (SMR = 1.66, 95%

28 CI = 0.71 to 3.27, 8 deaths), prostate cancer (SMR = 1.62, 95% CI = 0.77 to 2.97, 10

29 deaths), and leukemia (SMR = 2.31, 95% CI = 0.92 to 4.77, 7 deaths). For each tumor

30 site, the authors calculated SMRs for low- and high-exposed workers, low- and high-

1 exposed workers stratified by latency and/or exposure time, and for workers at the three

2 different factories.

3 SMRs for lung cancer were similar in low- (1.31; 11 vs. 8.4 expected deaths) and high-

4 exposure groups (1.39, 6 deaths vs. 4.3 expected), and were higher when the analysis was

5 restricted to workers whose time since first exposure was greater than 20 years (SMR =

6 2.02, [95% CI = 0.54 to 5.2], 4 deaths for the low-exposure group; SMR = 2.30, [95% CI

7 = 0.62 to 5.9], 4 deaths for the high-exposure group). The lung-cancer SMRs increased

8 again when the analysis was further restricted to workers with duration of exposure

9 greater than 10 years (SMR = 2.27, [95% CI = 0.54 to 6.6], 3 deaths for the low-exposure

10 group; SMR = 3.33, [95% CI = 0.90 to 8.5], 4 deaths for the high-exposure group).

11 However, only when the analysis combined all exposed workers with time since first

12 exposure greater than 20 years and duration of exposure greater than 10 years did the

13 excess lung-cancer mortality become statistically significant (SMR = 2.78, 95% CI =

14 1.11 to 5.72, 7 deaths). SMRs were the highest among workers in Factory A (1.71, 12

15 deaths vs. 7 expected) and were less than one among workers in Factory B and were 1.07

16 for factory C (based on 1 observed death). In both the total cohort and Factory A, SMRs

17 were somewhat higher among workers with exposure times from 1 to 4 years than

18 workers with 5 or more years of exposure.

19 With respect to leukemia, a higher SMR was found in the low-exposure group (2.94, 6

20 observed vs. 2 expected deaths) compared with the high-exposure group (1.01, 1

21 observed vs. 1 expected death). A statistically significant SMR for leukemia was found

22 with 1 to 4 years of exposure (SMR = 7.69, 95% CI = 2.49 to 17.95, 5 deaths); however,

23 the SMR for workers at Factory A with greater than 5 years of exposure was 1.21, 95%

24 CI 0.03 to 6.77, 1 death). A similar pattern, that is higher SMRs among workers with

25 shorter exposure times than longer exposure time, was observed among the entire cohort.

26 SMRs for leukemia were not calculated for different latency periods.

27 The SMR for prostate cancer was somewhat higher among the high-exposure group

28 (SMR = 2.05, 4 observed vs. 1.9 expected deaths) than the low-exposure group (SMR

29 =1.42, 6 observed vs. 4.2 expected deaths) and among workers with longer periods (> 5

1 years) of exposure; however, the risks were not higher among workers with longer

2 latency, and no significant SMRs were reported. No consistent exposure-response

3 patterns were found for tumors at other sites. [Subgroup analyses were limited by small

4 numbers of observed and expected deaths.]

5 *Strengths and limitations*

6 [Given the small size of the hard-metal production industry, this study examined a

7 relatively large cohort, with an overall expected lung cancer mortality of 12.7 deaths.

8 However, in absolute terms, the sample size was small, and when analysis was restricted

9 to workers with estimated eight-hour cobalt exposure greater than 5 $\mu g/m^3$, expected

10 lung-cancer mortality was only 4.3 deaths. Given these small numbers, the power to

11 detect an excess was very small. Another potential problem was due to the use of national

12 death rates; the largest and oldest factory (Factory A), which accounted for almost all

13 workers in exposure group 4, was located in the Stockholm area, where the lung cancer

14 rate was 30% above the national rate. Thus, the expected numbers of deaths for the high-

15 exposure group likely were underestimated, and the SMRs thus overestimated. The

16 authors also noted that most of the low-exposure groups were in Factory B, which was in

17 the countryside, and the use of national statistics would provide expected values that are

18 too high.

19 It is not clear from this paper whether complete job histories were available, but it seems

20 unlikely, given that the authors reported a 15% misclassification rate when 100 randomly

21 selected workers were reclassified by the same consultant who made the initial

22 classification. Potential confounding was not treated in any detail. A survey of this

23 workforce in the late 1970s showed their smoking habits not to differ from those of the

24 Swedish population, suggesting that confounding from smoking was not likely. Exposure

25 to other potential occupational carcinogens (such as asbestos or nickel) was not

26 discussed.]

27 Hogstedt and Alexandersson commented that the excess of leukemia, primarily in

28 Factory A (Stockholm) was difficult to explain. Excesses for cirrhosis of the liver and

29 circulatory organ diseases were also observed in the temporary employees in Stockholm.

1   The authors commented that temporary employees might have alcohol problems, poor

2   eating habits, and high consumption of tobacco, and might also have several high

3   occupational exposures in the various jobs. These workers often are given the least

4   attractive jobs with poor working conditions.

5   3.2.2   *Lasfargues* et al. *(1994)*

6   *Population and follow-up:*

7   Lasfargues *et al.* (1994) followed the mortality of 709 workers at a hard-metal producing

8   plant in central France from 1956 to 1990. This cohort also was included in the cohort

9   described by Moulin *et al*. (1998) (Section 3.2.3). Vital status was obtained from registry

10   offices at the birthplaces of subjects born in France and at the central French registry for

11   foreign-born workers. Workers whose vital status could not be determined were

12   considered lost to follow-up when they left the factory. Causes of death were obtained

13   from general practitioners and hospitals and were coded according to ICD-9. Expected

14   numbers of deaths by cause were based on national death rates, and SMRs were

15   calculated using standard life-table methods. Data on smoking habits (never-smokers, ex-

16   smokers, and current smokers) were obtained from medical records and interviews with

17   still active workers and were available for 81% of the workers.

18   *Exposure assessment*

19   Each worker was classified into one of the following exposure groups: group 1,

20   unexposed (mainly clerical workers); group 2, low exposure (maintenance workers

21   outside the hard-metal production workshops and hard-metal finishing workers using

22   protective devices [step 3]); group 3, medium exposure (hard-metal finishing workers not

23   using protective devices [step 3], workers machining unsintered materials with protection

24   [step 2 before sintering], and workers at the oven [step 2]); and group 4, high exposure

25   (workers involved in powder mixing, pressing, and machining of unsintered materials

26   without protection [step 2 production]). Eight-hour exposures to cobalt were measured in

27   this plant in 1983; levels for the groups defined above were as follows: group 2, less than

28   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

29   histories were available, each worker was assigned to one exposure group. Nonclerical

30   workers hired before 1974 for which no work-history information was available were

1   assigned to group 3. Duration of exposure was approximated by duration of employment

2   in the plant.

3   *Results*

4   Overall, there was a nonsignificant excess of all malignant neoplasms, due mainly to a

5   significant excess of lung cancer (SMR = 2.13, 95% CI = 1.02 to 3.93, 10 deaths) and a

6   nonsignificant excess in leukemia (SMR = 3.09, 95% CI = 0.37 to 11.14, 2 deaths). The

7   lung cancer excess was due mainly to a large excess in the high-exposure group (SMR =

8   5.03, 95% CI = 1.85 to 10.95, 6 deaths). The SMR for lung cancer among workers in the

9   high-exposure group whose time since first employment was 10 to 19 years was 6.79

10   (95% CI = 1.40 to 19.85, number of deaths not provided). In combined analysis of

11   smoking and exposure to hard metals; elevated SMRs for lung cancer were found among

12   never smokers with high exposure (SMR = 6.71, 2 deaths); current smokers with medium

13   (SMR = 9.20, 3 deaths) or high exposure (SMR = 15.14, 3 deaths); and unknown for

14   smoking status and high-exposure (SMR = 4.24, 1 death), [but these analyses were based

15   on small numbers of cases]. Lung cancer mortality did not increase with duration of

16   employment or time since employment. No excess in mortality was found for respiratory

17   disease (non-malignant).

18   *Strengths and limitations*

19   [For this small cohort of hard-metal workers, overall expected lung cancer mortality was

20   4.69 deaths. When the analysis was restricted to workers with an estimated daily cobalt

21   exposure above 15 $\mu g/m^3$, the expected number of lung cancer deaths was only 3.27.

22   Given these small numbers, the power to detect any significant excess was very small.

23   Nonetheless, a significantly elevated SMR was observed in the high-exposure group.

24   Complete job histories were not available, and duration of employment may be a poor

25   proxy for duration of exposure. The power for detecting a trend was very small given the

26   cohort size. Potential confounding was treated in some detail for smoking, as some

27   information on smoking habits was available for 9 of 10 workers who died of lung cancer

28   and 81% of the cohort members. The smoking habits of the cohort did not differ from

29   those of the French population, and two workers in the high-exposure group who died of

1   lung cancer were nonsmokers so that confounding by smoking is unlikely. Exposure to

2   other potential occupational carcinogens was not discussed.]

3   3.2.3   *Moulin* et al. *(1998)*

4   *Population and follow-up*

5   Moulin *et al*. (1998) studied the mortality of the workforce (N = 7,459) of all 10 French

6   hard-metal producing plants (most of which were located in eastern France). This cohort

7   included the cohorts studied by Lasfargues *et al*. (1994) (Section 3.2.2) and Wild *et al*.

8   (2000) (Section 3.2.4). A nested case-control study of lung-cancer mortality also was

9   conducted. The mortality of this population was followed from 1968 to 1991. Vital status

10   was obtained from registry offices at the birthplaces of workers born in France and at the

11   central French registry for foreign-born workers. Workers whose vital status could not be

12   determined were considered lost to follow-up when they left the factory. Causes of death,

13   coded according to ICD-8 until 1975 and ICD-9 thereafter, were obtained from the

14   central registry. Expected numbers of death by cause were based on national death rates,

15   and SMRs were calculated using standard life-table methods. Information on smoking

16   habits (never, former, or current smokers) was obtained from interviewing colleagues

17   (70.5% cases and 51.3% controls), relatives (11.5% cases and 9.11% controls) and the

18   subjects themselves (0% cases and 18.8% controls), and was summarized as ever vs.

19   never smoker.

20   In the nested case-control study, 3 controls for each worker who died of lung cancer were

21   sampled from the cohort, matched on sex and date of birth within 6 months. Job histories

22   were obtained for most cases (61 of 63) and controls (180 of 184), and smoking (ever vs.

23   never) for 82% of cases and 79% of controls. All exposure indices were lagged 10 years

24   to account for disease latency.

25   *Exposure assessment*. An industry-specific job-exposure matrix was created through

26   consensus of nine experts (epidemiologists, occupational physicians, industrial

27   hygienists, and industry representatives) using a Delphi method. Their assessment was

28   based on plant visits, historical description of the industrial processes, and interviews

29   with former workers. This assessment was blind with respect to existing exposure

30   measurements (for details see Moulin *et al.* 1997). The matrix included 320 combinations

1 of factory, job, and time period, to which were assigned "semiquantitative" estimates of

2 exposure to sintered (step 3) and unsintered hard-metal dust (step 2), cobalt alone (in the

3 cobalt powder production workshops), and tungsten carbide alone (in the tungsten

4 carbide production workshops) (step 1). Specifically, the combinations were assigned

5 exposure intensity codes on a scale of 0 to 9 (where 0 = non-exposed and 9 = highest

6 exposure) and exposure frequency scores (less than 10%, 10% to 50%, and over 50% of

7 working time). The matrix also included "yes/no" assessments of exposure to other

8 potential carcinogens, including PAHs, asbestos, silica, nitrosamines, benzene, arsenic

9 compounds, cadmium compounds, and certain chromium and nickel compounds.

10 It was not possible to assign a "typical exposure" value to the semiquantitative coding of

11 the matrix because there were no systematic exposure measurements. However, there

12 were exposure measurements available from 1971 to 1974 for certain workplaces of

13 certain factories. For these samples, cobalt semiquantitative exposure codes from the job-

14 exposure matrix were significantly correlated with the log-transformed measured cobalt

15 concentrations. The assessment was blind to these measurements.

16 *Results*

17 Overall, there was a nonsignificant excess of all malignant neoplasms (SMR = 1.07, 95%

18 CI = 0.94 to 1.21, 247 deaths) due to a borderline significant excess of lung cancer (SMR

19 = 1.30, 95% CI = 1.00 to 1.66, 63 deaths) and nonsignificant excesses of malignant

20 neoplasms of the upper digestive tract (SMR = 1.20, 95% CI = 0.77 to 1.79, 24 deaths),

21 esophagus (SMR = 1.22, 95% CI = 0.73 to 1.90, 19 deaths), and pleura (SMR = 1.98,

22 95% CI = 0.41 to 5.79, 3 deaths).

23 In the nested case-control study, the odds ratio (OR) for lung-cancer mortality following

24 simultaneous exposure to cobalt and tungsten carbide at exposure intensity levels of 2 or

25 higher (vs. 0 or 1) was 1.93 (95% CI = 1.03 to 3.62, 26 cases) after adjustment for other

26 cobalt exposure (exposure to cobalt alone or with agents other than tungsten carbide).

27 The OR increased significantly with duration of exposure (decades) and cumulative

28 exposure (quartiles based on intensity level times duration, not weighted by frequency),

29 and non-significant trends (P = 0.08) were observed for exposure level and frequency-

30 weighted cumulative dose. Significant ORs were observed for the highest quartiles for

1   cumulative exposure vs. the lowest exposure group, reaching 4.13 (95% CI = 1.49 to

2   11.47, 23 cases) for unweighted cumulative doses and 2.73 (1.02 to 7.26, 19 cases) for

3   frequency-weighted cumulative dose. In the subset of individuals with known smoking

4   habits (50 cases and 143 controls), adjustment for smoking or other potential confounders

5   did not change the trends and had little influence on the ORs. No excess morality was

6   found for non-malignant respiratory diseases.

7   *Strengths and limitations*

8   [The major strengths of this study were its relatively large size, its relatively good control

9   of potential confounders (both smoking and exposure to other potential occupational

10 carcinogens), and its semiquantitative exposure scale that allowed detection of exposure-

11 response relationships. Its main weaknesses were the heterogeneity of the industrial

12 processes among the various sites and the difficulty of retrospective exposure estimation.

13 Although the basic industrial process of production of cobalt–tungsten carbide powders

14 and hard metals is similar at different facilities, the exposure levels can be quite different,

15 as observed in the wide range of cobalt exposure measurements associated with each

16 semiquantitative code. For levels 2 through 5, based on the personal samples, the ratio of

17 the 97.5 to the 2.5 percentile ranged from 108 to 1,206. Therefore, it would be misleading

18 to identify a "typical dose" associated with an exposure level. Possibly even more

19 important is potential confounding by exposure to other agents, especially in the largest

20 cohort included in this study (described in Wild *et al.* 2000), which included workers

21 exposed to a wide range of other production processes, some of which involved other

22 cobalt exposures and exposure to other known carcinogens (see Section 3.3). In the

23 present paper these other exposures were summarized in the binary item "other cobalt

24 exposures."]

25 3.2.4   *Wild* et al. *(2000)*

26 *Population and follow-up*

27 Wild *et al.* (2000) followed the mortality of the workforce of a hard-metal producing

28 plant in eastern France from 1968 to mid 1992 (N = 2,860). This cohort was included in

29 the cohort described by Moulin *et al.* (1998) (Section 3.2.3). Vital status was obtained

30 from registry offices at the birthplaces of workers born in France and at the central

1   French registry for foreign-born workers. Workers whose vital status could not be

2   determined were considered lost to follow-up when they left the factory. Follow-up

3   continued until either the date of death or the person's 85th birthday [the reason for

4   selecting this age to end follow-up was not stated]. Causes of death, coded according to

5   ICD-8 until 1975 and ICD-9 thereafter, were obtained from the central registry. Expected

6   numbers of deaths by cause were based on regional death rates, and SMRs were

7   calculated using standard life-table methods. Exposure to smoking was obtained from

8   occupation health department records. The authors stated that this information was

9   "sketchy" until 1978, and thus was reassessed by a volunteer group of former workers.

10 *Exposure assessment*

11 The plant was established in the late 1940s. Hard-metal production co-existed with other

12 production processes involving cobalt, mostly based on powder metallurgy; these

13 included production of magnets, stainless steel, stellite, other sintered alloys of iron,

14 nickel, copper, and tin, and cobalt powder and tungsten carbide powder. Workshops were

15 categorized as non-exposed, hard-metal production before sintering, hard-metal

16 production after sintering, production of other sintered alloys, foundries, and powder

17 production. Detailed individual job histories were available, including jobs performed

18 within given workshops. The job-exposure matrix developed for the industry-wide study

19 by Moulin *et al.* (1998) was used to compute individual exposures and durations. All

20 exposure indices were lagged 10 years to account for disease latency.

21 *Results*

22 Overall, there was a nonsignificant excess of all malignant neoplasms among males

23 (SMR = 1.08, 95% CI = 0.90 to 1.30, 118 deaths), due mainly to a significant excess of

24 lung cancer (SMR = 1.70, 95% CI = 1.24 to 2.26, 46 deaths), and nonsignificant excesses

25 of malignant neoplasms of the upper digestive tract (SMR = 1.53, 95% CI = 0.84 to 2.57,

26 14 deaths), esophagus (SMR = 1.35, 95% CI = 0.62 to 2.57, 9 deaths), and pleura (SMR

27 = 2.44, 95% CI = 0.27 to 8.81, 2 deaths). No significant excesses for mortality from non-

28 malignant respiratory diseases were observed.

29 *By workshop:* For hard-metal production (without distinguishing between exposure to

30 sintered or unsintered hard metal) for males for lung cancer, the SMR was 1.93 (95% CI

1   = 1.05 to 3.23, 14 deaths). Higher SMRs were found for workers ever employed in pre-

2   sintering hard-metal production (SMR = 2.42, 95% CI = 1.10 to 4.59, 9 deaths) or only

3   employed in pre-sintering hard-metal production (SMR = 2.91, 95% CI = 1.06 to 6.34, 6

4   deaths). For workers ever employed in post-sintering hard-metal production, excess

5   mortality was relatively small (SMR = 1.28, 95% CI = 0.41 to 2.98, 5 deaths). SMRs

6   were nonsignificantly elevated for several other workshops (foundries, other alloys, and

7   cobalt powder production), but significantly elevated for the maintenance workshop

8   (SMR = 2.56, 95% CI = 1.28 to 4.59, 11 deaths). Although maintenance work was not

9   specific to any industrial process, the job-exposure matrix identified most maintenance

10   jobs as involving intermittent (low-frequency) high exposures to hard-metal dusts,

11   including the jobs of 10 of the 11 maintenance workers who died of lung cancer.

12   *By job-exposure matrix:* For all hard-metal exposure levels of 2 or higher (combined) for

13   males for lung cancer, the SMR was significantly elevated (SMR = 2.02, 95% CI = 1.32

14   to 2.96, 26 deaths). Significant SMRs (~2-fold) were also found for the highest exposure

15   quartiles for cumulative dose (both unweighted and frequency weighted); non-

16   significantly increased SMRs were found for the highest category of exposure duration

17   (2.65, 95% CI = 0.85 to 6.17, 5 deaths) and exposure score (2.80, 0. 76 to 7.16, 4 deaths).

18   The SMRs increased with exposure duration (P = 0.07), but test for trends for cumulative

19   exposure were not significant in models that adjusted for smoking and exposure to any

20   "IARC carcinogen" (defined as PAHs, silica, nickel compounds, chromium compounds,

21   or cobalt (without tungsten).

22   The SMR for subjects exposed to any IARC carcinogen was significantly elevated (SMR

23   = 2.05, 95% CI = 1.34 to 3.00, 26 deaths). In an internal estimation of relative risk (RR)

24   by Poisson regression, adjusted for smoking and exposure to any IARC carcinogen, the

25   RR increased significantly with duration of exposure to unsintered hard-metal dust at an

26   exposure level of 2 or higher. No increased RR was found for exposure to sintered hard-

27   metal dose (yes vs. no) in this model.

28   *Strengths and limitations*

29   [Although this cohort was smaller than that of Moulin *et al.* (1998), in which it was

30   included, hard-metal exposure was more precisely defined than in the industry-wide

1   study as the exposure was more homogeneous. The availability of job histories (and thus

2   exposure estimates) for all cohort members allowed for a more powerful internal

3   comparison of risk. The main limitations of this study were the lack of direct

4   measurements of exposure to hard-metal dust and co-exposure to several other

5   production processes (involving other cobalt exposures and exposure to other IARC

6   carcinogens), so that limited confounding of the internal dose-response relationship is

7   possible.]

8   **3.3   Discussion**

9   The populations in the three French studies overlapped to some extent, as the cohort

10 followed by Moulin *et al*. from 1968 to 1991 included most of the populations followed

11 by Lasfargues *et al*. from 1956 to 1989 and Wild *et al*. from 1968 to 1992. The latter two

12 cohorts were, however, completely independent. [Thus, if we are looking for completely

13 independent observations, one should either contemplate these two papers and dismiss

14 the paper by Moulin *et al*. (1998) or, alternatively, dismiss them and consider only the

15 paper by Moulin *et al*. (1998).]

16 3.3.1   *Confounding*

17 In all four studies, the smoking habits of the cohort were similar to those of the reference

18 population. [In the studies by Hogstedt and Alexandersson (1990) and Lasfargues *et al.*

19 (1994) smoking was controlled for only indirectly.] Moulin *et al.* suggested the

20 possibility of an interaction between exposure to hard-metal dust and smoking (based on

21 a nonsignificant interaction in the subset of workers with known smoking habits in the

22 case-control study). However, both Lasfargues *et al.* and Wild *et al.* observed a small

23 excess of lung cancer even among nonsmoking workers exposed to hard-metal dust.

24 Neither Hogsted and Alexandersson nor Lasfargues *et al.* discussed exposure to other

25 occupational carcinogens. Wild *et al*. considered exposure to a number of other potential

26 carcinogens, and their internal RR analysis, which showed significantly increased risk

27 with increasing duration of exposure to hard-metal dust, was adjusted for both smoking

28 and exposure to other carcinogens (grouped as "any IARC carcinogen"). Moreover, the

29 SMR in this study was significantly elevated in a subcohort not exposed to other

30 carcinogens (workers employed only in pre-sintering hard-metal production). Moulin *et*

1   *al*. also considered other potential carcinogens, and the analysis of the nested case-control

2   study, which showed a significantly increased OR with increased cumulative hard-metal

3   exposure, was adjusted for both smoking and other cobalt exposure.

4   3.3.2   *Exposure-response relationships*

5   [In the studies by Hogstedt and Alexandersson (1990) and Lasfargues *et al*. (1994),

6   exposure assessment was relatively crude. Although these cohorts were too small to have

7   any power to detect a significant trend, the largest SMRs were reported for the highest

8   exposure categories. For the larger cohorts of Moulin *et al*. and Wild *et al.*, significant

9   exposure-response trends were observed; however, because the former study included the

10   cohort of the latter study, these observations cannot be considered to be independent.]

11   Moulin *et al*. reported that the ORs in the nested case-control study increased

12   significantly with increasing cumulative exposure (OR = 4.13, 95% CI = 1.49 to 11.5, 23

13   cases in the highest exposure quartile). This exposure-response relationship was based on

14   a semiquantitative exposure code for hard-metal exposure obtained from an expert-based,

15   job-exposure matrix. Although these semiquantitative ratings were significantly

16   correlated (P = 0.015 for long-duration personal or area samples and P < 0.0001 for

17   short-duration area sampling) with cobalt measurements in the French hard-metal

18   industry, very few long-duration personal exposure measurements were available for

19   exposure intensity levels over 5 (on the scale from 0 to 9), and the range of measured

20   exposures within each level was very broad. Wild *et al*. found significantly increased

21   risks among workers in the highest exposure quartiles for exposure score and cumulative

22   exposure (both unweighted and frequency weighted). In internal analyses that adjusted

23   for smoking and exposure to other carcinogens, the RR increased significantly with

24   duration of exposure to unsintered hard-metal dust.

25   3.3.3   *Human cancer studies evaluating other exposures to cobalt*

26   The IARC 2006 monograph evaluated two studies on exposure to cobalt not related to

27   cobalt–tungsten carbide hard powders and hard metals. A study by Mur *et al*. (1987)

28   found an excess of lung cancer in a cobalt production workshop, which was not

29   confirmed in a follow-up study by Moulin *et al*. (1993b). (Excesses of lung cancer

30   mortality were observed among maintenance workers; however, the IARC working group

1   noted that this might be explained by other carcinogenic exposures such as smoking or

2   asbestos). Tuchsen (1996) studied a cohort of Danish porcelain workers exposed to

3   aluminate spinal and/or cobalt silicate at two factories. Although a significantly increased

4   of risk of lung cancer was observed in exposed workers compared with the Danish

5   population, lung cancer risk was also increased in a reference group of non-exposed

6   workers at one of the factories; the relative risk ratio between exposed and reference

7   group was 1.2 (95% CI = 0.4 to 3.8).

8   In addition, two studies of the hard-metal industry also evaluated exposure to cobalt that

9   did not include tungsten carbide. Moulin *et al*. (1998) reported a two-fold increased risk

10   for lung cancer mortality for exposure to cobalt alone or simultaneously with agents other

11   than tungsten carbide. Wild *et al*. (2000) observed a slight excess of lung cancer mortality

12   (2 deaths) among workers in the cobalt powder production workshop.

13   **3.4   Summary**

14   Workers in the cobalt–tungsten carbide powders and hard-metal (hereafter called hard

15   metals) industry are exposed to either presintered or sintered hard-metal particles. Four

16   cohort studies (although not independent) were identified that evaluated exposure to

17   cobalt–tungsten carbide powders and hard metals and cancer mortality. These studies

18   included a (1) a cohort study of Swedish workers at three hard-metals facilities (Hogstedt

19   and Alexandersson 1990), (2) a small cohort of French hard-metal manufacturing

20   workers (Lasfargues *et al.* 1994), (3) a multi-plant cohort study of workers at 10 hard-

21   metal producing factories in France, which also included a nested case-control analysis

22   (Moulin *et al.* 1998), and (4) a cohort study of the largest factory of the multi-plant

23   French study (Wild *et al.* 2000). The multi-plant study also included workers studied by

24   Lasfargues *et al.* All of the studies attempted to evaluate exposure-response relationships,

25   although the exposure assessments by Hogstedt and Alexandersson and Lasfargues *et al.*

26   were crude. Both Wild *et al.* and Moulin *et al.* attempted to control for smoking and/or

27   other occupational exposure.

28   All four studies reported an increased lung cancer risk, with significantly increased lung

29   cancer mortality either in the whole cohort or in among workers with higher or longer

1   exposure, or longer latency. Hogstedt and Alexandersson found significant excess lung

2   cancer mortality in a subgroup of long-latency, long-exposure-duration workers, and

3   Lasfargues *et al.* found a five-fold significantly elevated SMR in their high-exposure

4   group. Moulin *et al.* (1998) found an overall increase in lung cancer mortality of

5   borderline statistical significance and significantly increased risk for exposures levels

6   higher than level 2 compared with the lowest level. In the nested case-control study, the

7   risk of lung cancer increased significantly with duration of exposure ($P = 0.03$) and

8   cumulative dose (unweighted) ($P = 0.01$) and non-significantly increased with exposure

9   level ($P = 0.08$) and cumulative dose (frequency weighted) ($P = 0.08$). Adjustment for

10   smoking or known or suspected carcinogens did not change the ORs. Wild *et al.* (2000)

11   found significantly elevated lung cancer SMRs among all workers and workers ever

12   employed in pre-sintering workshops, and among the highest exposure category

13   (exposure score, unweighted cumulative exposure, weighted cumulative exposure) to

14   hard metal dusts. In models controlling for smoking and exposure to any "IARC

15   carcinogen" (PAHs, silica, nickel compounds, chromium compounds, or cobalt without

16   tungsten), the test for trends was of borderline significance for exposure duration and was

17   not significant for exposure level or cumulative dose. In analyses that evaluated exposure

18   to unsintered hard metals, a significantly increased trend for duration of exposure was

19   found in models that controlled for smoking and exposure to any "IARC carcinogen." No

20   increased risk for exposure to sintered metals was found in this model.

21   Hogstedt and Alexandersson was the only study to evaluate risks for tumors sites other

22   than lung in more details (e.g., they evaluated risks by exposure groups, exposure

23   duration, and individual factory). They reported a significant excess risk for leukemia

24   among workers employed at one of the factories and exposed for less than 5 years, but

25   not among longer exposed workers. A non-significant excess of leukemia was found

26   among the small cohort study of French workers (Lasfargues *et al.*), but not among the

27   larger studies (Moulin *et al.*, Wild e*t al.*). Non-significant excesses of cancer of the

28   esophagus (Lasfargues *et al.*, Moulin *et al.*, Wild *et al.*), upper GI (Moulin *et al.*, Wild *et*

29   *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
 	
Sweden
	Historical mortality cohort study 1951–1982	All workers at 3 hard-metal producing factories who had worked at least 1 yr in hard-metal production (N = 3,163)
		
		Causes of death from national registry
		
		National death rates
			Workers were divided into two exposure groups:
			
			Low exposure in production workshops without direct involvement in production (Groups 1 and 2) (< 5 μg/m³)
			
			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)
			
			Group 3: 10–30 μg/m³;
			Group 4: 10–11,000 μg/m³
				SMR (95% CI); number of deaths
				Overall 0.96 (0.85–1.07); 292
				Cancers with excess mortality
				  (all exposed men [1951 to 1982])
				leukemia 2.31 (0.92–4.77); 7
				prostate 1.62 (0.77–2.97); 10
				pancreas 1.66 (0.71–3.27); 8
				
				Lung cancer
				total cohort 1.34 (0.77–2.13); 17
				≥ 10-yr exposure and > 20-yr latency
				         2.78 (1.11–5.72); 7
				> 20-yr exposure level and latency
				low 2.02 [0.54–5.2]; 4
				high 2.35 [0.064–6.02]; 4
				10-yr exposure duration and exposure level
				low 2.27 [0.54–6.6]; 3
				high 3.33 [0.90–8.5]; 4
					[Some exposure misclassification likely]
					
					High mortality for several causes among short-term (< 5 years) workers
					
					Factory A was the oldest factory, with the highest exposures
					
					No adjustment for smoking, but a survey of this workforce suggested that the number of smokers among active workers was close to national average

Reference	Study design and follow-up	Population and methods	Exposure	Effect: SMR, OR, or RR	Comments
Lasfargues *et al.* 1994 France	Historical mortality cohort study 1956–1989	All male workers of a hard-metal producing factory who had worked at least 1 yr at this site (N = 709) Causes of death from general practitioners and hospital records National death rates Smoking from medical records and personal interviews	Time since first employment and duration of employment Exposure to hard-metal dust in four groups (cobalt exposure, $\mu g/m^3$): 1. non-exposed 2. low (maintenance), < 10 3. medium (sintered), 15–40 4. high (unsintered), > 50 No complete work histories	SMR (95% CI); number of deaths *Overall mortality* 1.05; 75 deaths *Cancers with excess mortality* Entire cohort leukemia 3.09 (0.37–11.14); 2 esophagus 1.90 (0.39–5.55); 3 lung 2.13 (1.02–3.93); 10 No subgroup analysis for cancers other than lung (numbers of cases were small) *Lung Cancer* Exposure Category no 1.52 (0.04–8.48); 1 low 0.00 (0.00–5.18); 0 medium 1.44 (0.30–4.21); 3 high 5.03 (1.85–10.95); 6 Exposure duration (yr) 1–9 3.39 (1.36–6.98); 7 10–19 1.23 (0.03–6.84); 1 ≥ 20 2.52 (0.06–14.02); 1 Time since first employment (yr) 1–9 1.86 (0.05–10.39); 1 10–19 3.65 (1.19–8.53); 5 ≥ 20 2.17 (0.45–6.34); 3	High mortality from suicide (SMR = 3.66, 13 deaths), especially in high-exposure groups [Some exposure misclassification likely] Numbers of smokers among active workers close to national average Lung cancer excess among high-exposure nonsmokers (SMR = 6.71; 2 deaths)

Reference	Study design and follow-up	Population and methods	Exposure	Effect: SMR, OR, or RR	Comments
Moulin *et al.* 1998 France	Historical mortality cohort study and nested case-control study 1968–1991	*Cohort study* All workers at 10 hard-metal producing factories who had worked at least 3 months at any site (N = 7,459) Causes of death from national registry National death rates *Case-control study* Cases: 61 Controls: 180 For each lung cancer case, 3 controls were sampled from the cohort, matched by sex and year of birth Job histories and smoking obtained from administrative and medical records and interviews with colleagues	An industry-specific job-exposure matrix was used to assign semiquantitative exposure intensity codes (0 = non-exposed to 9 = highest exposure) and frequency codes to sintered and unsintered hard-metal dust Yes/no assessment of exposure to several other potential carcinogens based on historical description of the industrial processes The semiquantitative exposure intensity levels significantly correlated with available measurements of cobalt Exposure of cases and controls was based on 10-year-lagged maximal exposure intensity, duration of exposure intensity, duration of exposure, and frequency-weighted and unweighted cumulative doses	*Cohort Study* SMR (95% CI); number of deaths overall 0.93 (0.87–1.01); 684 upper GI 1.20 (0.77–1.79); 24 esophagus 1.22 (0.73–1.90); 19 pleura 1.98 (0.41–5.79); 3 lung 1.30 (1.00–1.66); 63 *Nested case-control study- lung cancer* OR (95% CI); cases/controls <u>Exposure level</u> 2+ vs. 0–1 1.93 (1.03–3.62); 35/81 0–1 1.0; 26/99 2–3 3.37 (1.19–9.56); 8/12 4–5 1.54 (0.76–3.12); 19/55 6–9 2.79 (0.96–8.10); 8/14 test for trend, $P = 0.08$ <u>Exposure duration (yrs) (levels 2+)</u> non-exposed 1.0; 26/99 ≤ 10 1.61 (0.78–3.34); 19/52 10–20 2.77 (1.12–6.82); 12/20 ≥ 20 2.03 (0.49–8.51); 4/9 test for trend, $P = 0.03$ <u>unweighted cumulative dose</u> < 32 1.0; 6/46 32–142 2.64 (0.93–7.47); 16/43 143–299 2.59 (0.88–7.6); 16/45 >299 4.13 (1.49–11.47); 23/46	No increased SMR for any other cause of death *unweighted cumulative dose* (same value for occasional and fulltime exposure, thus favoring peak exposures) [The exposure measurements were insufficient to quantitatively characterize the exposure levels] [Some exposure misclassification was likely, both from the job-exposure matrix and from the actual job histories] The smoking OR was smaller than expected, due to a large percentage (20%) of nonsmokers among workers who died of lung cancer. [This points to a possible misclassification of smoking] OR for other cobalt exposure (cobalt alone or with other agents other than tungsten carbide) Levels 2–9/ vs. 0-1 2.21 (0.99–4.90)/15/30

Reference	Study design and follow-up	Population and methods	Exposure	Effect: SMR, OR, or RR	Comments
				test for trend, $P = 0.01$	
				Frequency-weighted cumulative dose	
				< 4 1.0; 8/45	
				4–27 2.28 (0.86–6.06); 20/45	
				27–164 1.85 (0.66–5.20); 14/45	
				> 164 2.73 (1.02–7.26); 19/45	
				Test for trend, $P = 0.08$	
Wild *et al.* 2000 France	Historical mortality cohort study 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) Causes of death from national registry Regional death rates Complete job histories from company records Smoking obtained from medical records and validated by a group of former workers	The job-exposure matrix of Moulin *et al.* (1997) was used. 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. Exposure to other potential carcinogens was summarized as yes/no. The data allowed analysis by workshops: non-exposed workshops, pre-sintering hard-metal production, post-sintering hard-metal production, and other exposed.	SMR (95% CI); number of deaths *Cancers with excess mortality, males* upper GI tract 1.53 (0.84–2.57); 14 esophagus 1.35 (0.62–2.57); 9 pleura 2.44 (0.27–8.81); 2 lung 1.70 (1.24–2.26); 46 *Lung Cancer* By workshop (ever employed) pre-sintering 2.42 (1.10–4.59); 9 post-sintering 1.28 (0.41–2.98); 5 By job-exposure matrix exposure score (levels) 0–1 1.41 (0.86–2.17); 20 2–3 2.10 (0.84–4.33); 7 4–5 1.85 (1.03–3.04); 15 ≥ 6 2.80 (0.76–7.16); 4 ≥ 2 2.02 (1.32–2.96); 26 Test for trend, $P = 0.17$ exposure duration (yr) none 1.41 (0.86–2.17); 20	Overall mortality close to expected (SMR = 1.02, 399 deaths) No increased SMR for any other cause of death No quantitative estimates of hard-metal exposure were available [The availability of full job histories and the participation of the former industrial physician probably limited exposure misclassification] The number of smokers in the cohort was close to the national average in 1980. The SMR among nonsmokers was larger than expected (SMR = 1.35, 7 deaths) [The thorough search for information on smoking habits probably limited

Reference	Study design and follow-up	Population and methods	Exposure	Effect: SMR, OR, or RR	Comments
				< 10 1.57 (0.78–2.81); 11 11–19 2.51 (1.20–4.61); 10 > 20 2.65 (0.85–6.17); 5 Test for trend, $P = 0.07$ unweighted cumulative dose 1 1.17 (0.50–2.30); 8 2 1.66 (0.83–2.97); 11 3 1.61 (0.80–2.88); 11 4 2.36 (1.35 –3.83); 16 Test for trend, $P = 0.23$ weighted cumulative dose 1 1.33 (0.61 – 2.53); 9 2 1.62 (0.81 – 2.89); 11 3 1.78 (0.92 – 3.10); 12 4 2.06 (1.1 3 – 3.46); 14 Test for trend, $P = 0.37$ Poisson regression, adjusted for smoking and exposure to other potential carcinogens RR (95% CI) for hard metal unsintered 1.43 (1.03–1.98) sintered 0.75 (0.37–1.53)	smoking misclassification] 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 5.5.

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5 Other Relevant Data

This section discusses relevant mechanistic and other 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), mechanistic studies (Section 5.4), a brief review of the toxicity, carcinogenicity, and genotoxicity of cobalt or tungsten individually (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 Section 2.3). [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. Scansetti *et al.* (1994, 1998) measured cobalt in the urine of workers in the cobalt–tungsten carbide hard-metal industry, but found no correlation with levels of cobalt in ambient air. Other studies have reported a correlation between cobalt concentrations in the urine and air (see Section 2.3). For example, Lison *et al.* (1994) reported a positive correlation between log cobalt in the urine and log cobalt in the air for 10 workers in a cemented-carbide factory. Cobalt or tungsten also 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

1   blood, pubic hair, and toenails of cobalt–tungsten carbide hard-metal workers, and

2   Kazantzis (1986) detected tungsten in the feces of 10 hard-metal production workers.

3   Scansetti *et al.* (1994) (in a study of Italian hard-metal production workers) demonstrated

4   that cobalt could be absorbed through the skin. The urinary concentration of cobalt

5   increased by an order of magnitude in subjects who each held one of their hands in a box

6   filled with either freshly mixed cobalt–tungsten carbide powder (about 5% to 15% cobalt

7   and 85% to 95% tungsten carbide) or waste dry powder.

8   After absorption, cobalt is distributed but does not accumulate in any specific organ

9   except for the lung after inhalation of insoluble particles (IARC 2006). The particles

10 present in these industries usually are of respirable size [$\leq 10\mu m$], indicating that they

11 potentially are deposited throughout the respiratory tract, including in the alveoli. Studies

12 in humans indicate that when cobalt–tungsten carbide hard-metal particles are deposited

13 in the lung, cobalt metal is rapidly solubilized, cleared from the lung, distributed in the

14 body, and excreted in urine; whereas, tungsten carbide particles persist longer in lung

15 tissue (reviewed by IARC 2006, Lison 1996, Lison *et al.* 1996). Particles containing

16 cobalt and tungsten carbide have been found in the lungs of exposed workers (see Section

17 2.3). Tungsten and other particles (including cobalt, silicon, aluminum, and titanium)

18 were detected in human lung tissue from 3 workers employed in the metal- and tool-

19 cutting and grinding industries and suspected to have occupationally induced lung disease

20 (Stettler *et al.* 1983). Rizzato *et al.* (1986) reported high concentrations of tungsten and

21 cobalt, along with tantalum, in lung specimens from an Italian man who had worked for

22 13 years grinding hard metals to sharpen tools. Rüttner *et al.* (1987) analyzed dust in lung

23 tissue from lung biopsies (N = 7) or whole lungs from autopsies (N = 9) of 16 metal

24 grinders exposed to hard metals for 5 to 44 years and found small or trace amounts of

25 cobalt, tungsten, or both metals in 14 of 16 samples. Schwarz *et al.* (1998) evaluated 14

26 workers exposed to dust containing hard metals and aluminum oxide. Microchemical

27 analysis of transbronchial biopsies in five workers showed a high lung burden of metal

28 particles. Tungsten was found in all five workers and was associated with tantalum,

29 titanium, aluminum, and iron. Cobalt was found in one worker.

1   Apostoli *et al.* (1994) reported a diphasic excretion of cobalt by workers exposed to

2   cobalt powders. Peak elimination occurred about 2 to 4 hours after exposure and

3   decreased over the following days. Torra *et al.* (2005) also reported a multiphasic pattern

4   for cobalt excretion by hard-metal workers with a rapid first stage of elimination (half-

5   life of 21 hours) and a slower second phase (half-life of 9 days). Torra *et al.* (2005)

6   reported a multiphasic pattern for cobalt excretion by hard-metal workers with a rapid

7   first stage of elimination (half-life of 21 hours) and a slower second phase (half-life of 9

8   days).

9   5.1.2   *Experimental animals*

10   Similar to humans, cobalt–tungsten carbide hard-metal particles are deposited in the lung,

11   cobalt metal is rapidly solubilized, cleared from the lung, distributed in the body, and

12   excreted in urine; whereas, tungsten carbide particles persist longer in lung tissue (

13   reviewed by Lison 1996). Lasfargues *et al*. (1992) reported that rats administered cobalt

14   as cobalt–tungsten carbide intratracheally excreted significantly greater amounts of cobalt

15   in the urine compared with rats administered pure cobalt. The authors suggested that

16   cobalt has a greater bioavailability when combined with tungsten carbide. Lison and

17   Lauwerys (1994) reported that at 6 hours, rats exposed to cobalt powder intratracheally

18   excreted cobalt at a much lower rate than rats exposed to cobalt–tungsten carbide powder,

19   but at 48 hours excretion was almost identical, and no significant difference was seen on

20   day 7. The authors also measured cobalt concentrations in the lung. After day 1, lung

21   concentrations of cobalt were two times higher in rats administered cobalt as compared

22   with cobalt–tungsten carbide; however, after day 7, the mean concentration of the metal

23   retained in the lung had decreased significantly to almost the same level in both groups.

24   5.1.3   *In vitro studies*

25   *In vitro* experiments with cobalt–tungsten carbide dust (71.4% cobalt and 24% tungsten),

26   radioisotopes (^{60}Co and ^{187}W) have characterized the interaction of cobalt and tungsten

27   with human blood and homogenized lung tissue (Edel *et al.* 1990). Cobalt was highly

28   soluble, especially in the lung cytosol and plasma. Three biochemical pools were

29   identified for cobalt. More than half (56%) of the dissolved cobalt was associated with

30   low molecular weight components and represented the diffusible and highly mobile

1 fraction. About 34% was associated with proteins with molecular weights of 70,000 to

2 80,000 Daltons, and 8% was associated with high-molecular-weight components. The

3 authors reported that tungsten had a very low solubility and low affinity for plasma or

4 tissue proteins, thus, they concluded that the small amounts of solubilized tungsten are

5 highly mobile. The authors also concluded that ability of cobalt and tungsten to dissolve

6 in body fluids is consistent with the transport of the metals from the lung to other tissues

7 such as pubic hair and toenails, and their presence in the urine of exposed individuals (see

8 above and Section 2.4). Lison and Lauwerys (1992) investigated the solubilization of

9 cobalt from different powders in murine macrophages *in vitro* and determined that the

10 solubilization of cobalt powders increased by a factor of 4 in the presence of tungsten,

11 which is consistent with the i*n vivo* findings reported by Lasfargues *et al*. (1992). Lison *et*

12 *al.* (1995) also reported increased solubility of cobalt in the presence of tungsten-carbide.

13 5.1.4   *Cobalt metals, cobalt compounds and tungsten metal and tungsten compounds*

14 Information on the biological fate of cobalt metal and cobalt compounds and of tungsten

15 metal and tungsten compounds other than the carbide supports the conclusion that cobalt

16 and tungsten are absorbed after either ingestion, inhalation, or dermal exposure (Elinder

17 and Friberg 1986, Kazantzis 1986, Linnainmaa and Kiilunen 1997). Studies in workers

18 exposed to cobalt suggest that the absorption rate of various cobalt compounds is

19 probably dependent on their solubility in biological fluids and in the alveolar

20 macrophages. Exposure to less soluble cobalt compounds was associated with lower

21 absorption rates (and probably a longer retention time in the lung) than absorption rates

22 after exposure to more soluble cobalt containing particles (such as hard-metal particles)

23 (Lison *et al.* 1994, Lison and Lauwerys 1994, as cited in IARC 2006). Both elements

24 distribute primarily to the lung after inhalation and to the liver after ingestion. Tungsten

25 also distributes to bone (Leggett 1997). Persson *et al.* (2003) reported that intranasal

26 administration of $^{57}Co^{2+}$ in rats resulted in uptake of the metal in the olfactory mucosa

27 with subsequent transport to the olfactory bulbs of the brain. Low levels of cobalt

28 migrated into the interior of the bulbs and the anterior parts of the olfactory cortex.

29 Limited evidence is available for metabolism of cobalt to organically complexed forms *in*

30 *vivo* (Gallorini *et al.* 1994), but no corresponding information on metabolism of tungsten

31 was found. Both elements are excreted primarily in the urine (Kazantzis 1986, Lison *et*

1   *al.* 1994). The biological half-life of cobalt is independent of exposure route. Most is

2   eliminated within days, but about 10% has a biological half-life of 2 to 15 years (Elinder

3   and Friberg 1986).

4   **5.2   Toxicity**

5   This section reviews the primary toxic effects of hard-metal particles in humans and

6   experimental animals, as well as the enhanced cytotoxicity produced by the interaction of

7   cobalt–tungsten carbide particles. The most common toxic effects occur at the site of

8   contact or deposition (skin and respiratory system). These effects include contact

9   dermatitis and bronchial asthma, which likely result from immunological sensitization to

10 cobalt, and hard-metal lung disease (IARC 2006). Occupational inhalation exposure to

11 cobalt–tungsten carbide hard-metal dust also is associated in some workers with the

12 occurrence of hard-metal disease, a giant-cell interstitial pneumonia that can develop into

13 pulmonary fibrosis, with a potentially fatal outcome. Extrapulmonary effects reported in

14 humans include memory loss, heart disease, and Goodpasture's syndrome.

15 [Goodpasture's syndrome is an autoimmune disorder that affects the lungs and kidneys. It

16 is rapidly progressive and usually fatal.] Systemic effects are not believed to be caused by

17 the metallic particles themselves, but may occur from the release of cobalt ions into the

18 blood or indirectly from lung damage (IARC 2006).

19 5.2.1   *Humans*

20 *Contact dermatitis*

21 Allergic contact dermatitis of the face, ears, and neck has been reported in hard-metal

22 workers (Dooms-Goossens *et al.* 1986). Fischer and Rystedt (1985) reported that 10% of

23 776 workers examined at a hard-metal factory had hand eczema while 15% had irritant

24 reactions. The authors noted that hand eczema has a more protracted course and is more

25 inflammatory than irritant reactions. Of more than 1,000 workers who had left the

26 industry during the previous 10 years, 87 had hand eczema; although, the cumulative

27 incidence of hand eczema for those 10 years was estimated at 17%. More than half of the

28 cases of hand eczema, and about 67% of the cases of irritant reactions occurred during

29 the first year of work. The highest risk was associated with grinding activities were

30 exposure to cutting oils and fluids was high. Linnainmaa *et al.* (1997) investigated

1   respiratory symptoms and dermatoses among grinder and brazers of hard-metal and

2   stellite blades. This study included 108 workers involved in the manufacture or

3   maintenance of tools, 116 saw filers in the mechanical wood-processing industry, and

4   two reference groups. The cobalt-exposed workers did not have a higher incidence of

5   hand dermatoses or symptoms of metal allergy than the unexposed workers. Sjögren *et*

6   *al.* (1980) reported concurrent contact eczema and interstitial pulmonary disease in four

7   case reports of workers exposed to hard metals during grinding operations. In each case,

8   the eczema first appeared within a few months of starting work in the wet grinding area.

9   *Respiratory effects*

10 Chronic exposure to mineral dust in the workplace can result in chronic bronchitis,

11 asthma, or emphysema. Specific respiratory effects from cobalt–tungsten carbide

12 exposure include bronchial asthma and hard-metal lung disease, characterized by

13 interstitial lung fibrosis. Although both diseases are considered relatively uncommon

14 (Meyer-Bisch *et al.* 1989, Sprince *et al.* 1988), occupational asthma as a result of cobalt

15 exposure has a greater frequency of occurrence than hard-metal disease (Cugell 1998,

16 Nemery *et al.* 2001).

17 Occupational asthma can occur as a result of cobalt sensitivity in workers exposed to

18 hard-metal dust (Shirakawa *et al.* 1989). It has been hypothesized that cobalt combines

19 with protein to produce a hapten allergen eliciting a type I hypersensitivity reaction

20 through the production of IgE antibodies (Skirakawa *et al.* 1989, Sjögren *et al.* 1980).

21 Shirakawa *et al.* (1988) measured specific IgE antibodies to cobalt-conjugated human

22 serum albumin in sera of 6 out of 12 hard-metal workers with a confirmed respiratory

23 sensitivity to cobalt. In a follow-up study (Shirakawa *et al.* 1989), 8 workers with

24 occupational asthma were shown to be sensitive to cobalt exposure, but only 4 were

25 positive for IgE antibodies specific to cobalt exposure. The authors noted that hard-metal

26 asthma may be a complex syndrome involving several types of sensitivity reactions,

27 including an IgE-mediated mechanism in some people.

28 Some authors use the term "hard-metal lung disease" to refer to all respiratory diseases

29 resulting from exposure to hard-metal dust, while others restrict the term to parenchymal

1 manifestations in hard-metal workers, exclusive of obstructive disorders (Kelleher *et al.*

2 2000). Further, the medical terminology used for the interstitial lung pathology observed

3 as a result of hard-metal and cobalt dust exposures has been has been described as

4 "confusing" (IARC 2006, Nemery *et al.* 2001). The earlier literature usually referred to

5 the disease as a pneumoconiosis; however, hard-metal disease differs from other mineral

6 pneumoconioses in that it is due to individual susceptibility, rather than from a

7 cumulative dust burden in the lungs (Nemery *et al.* 2001, Sjögren *et al.* 1980).

8 Hypersensitivity to cobalt alone can lead to contact dermatitis and hypersensitivity

9 pneumonitis, which can progress with continued exposures to interstitial fibrosis in the

10 lungs (Cugell 1998). However, unlike most other occupationally-derived airway irritants

11 and allergens, inhalation exposure to hard metals can lead to irreversible effects on the

12 lung parenchyma, resulting in interstitial fibrosis and giant-cell pneumonia (Nemery *et al*

13 2001). Giant-cell interstitial pneumonia is unique to hard-metal disease and considered

14 pathognomonic (IARC 2006, Ohori *et al.* 1989).

15 Recent experimental and epidemiological evidence suggests that this disease is caused by

16 the interaction of cobalt metal with tungsten carbide particles (reviewed by Lison *et al.*

17 1996). Hard-metal lung disease also has been described in workers exposed to cobalt

18 from diamond-coated polishing disks, and some older studies suggested that cobalt (and

19 not tungsten carbide) caused the respiratory effects observed in hard-metal workers

20 (Davison *et al.* 1983, Harding 1950, Sprince *et al.* 1984). However, only rare cases of

21 interstitial disease have been reported in workers exposed to cobalt alone and there are

22 many more workers exposed to cobalt alone than hard metals. Linna *et al.* (2003) found

23 no cases of hard-metal disease or fibrosing alveolitis among 110 cobalt production

24 workers exposed to cobalt but not to hard metals. Lison and coworkers (Lison 1996,

25 Lison *et al.* 1996b) concluded in reviews of the epidemiological literature that interstitial

26 lung disease occurs only among hard-metal and diamond workers and suggested a role

27 for simultaneous inhalation of other compounds such as tungsten carbide or diamond dust

28 in addition to cobalt. The occurrence of both fibrosing alveolitis and lung cancer in hard-

29 metal workers has been suggested to be related mechanistically, conceivably involving

30 oxidative damage and/or inflammatory events (IARC 2006). In addition, Bouros *et al.*

31 (2002) reported than an excessive relative risk of lung cancer has been found in patients

1   with pulmonary fibrosis compared with the general population; however, the

2   pathogenesis of lung cancer in these patients is unclear.

3   Although the pathogenesis of giant-cell interstitial pneumonia is unknown (Chiappino

4   1994, Nemery *et al.* 2001), involvement of the immune system has been proposed

5   (Ruediger 2000). Moriyama *et al.* (2007) investigated the distribution of inhaled hard-

6   metal particles and reactive inflammatory cells in lung tissues from 17 patients with

7   hard-metal lung disease. Tungsten and cobalt (especially tungsten) had accumulated in

8   the centrilobular fibrotic lesions of the patients but not in the controls. Further, CD163^{+}

9   macrophages co-localized with tungsten particles within the centrilobular fibrotic lesions,

10   and CD8^{+} lymphocytes also were distributed in and around the fibrotic lesions. [CD8^{+}

11   lymphocytes are a subset of T lymphocytes that can release cytotoxic factors such as

12   reactive oxygen species. CD163^{+} macrophages can engulf foreign particles.] The authors

13   noted their data provided evidence that both CD163^{+} macrophages and CD8^{+}

14   lymphocytes have a role in the pathogenesis of fibrotic alveolar lesions. Frost *et al.*

15   (1993) suggested an autoimmune mechanism for giant-cell interstitial pneumonia based

16   on recurrence of the disease in a transplanted lung despite the absence of any further

17   industrial exposure. Hahtola *et al.* (2000) described a case of allergic alveolitis

18   accompanied by rheumatoid arthritis, another disease resulting from an abnormal

19   immune response, in a woman whose trade was hard-metal sharpening. Other case

20   reports have demonstrated an association between hard-metal disease and the expression

21   of the cytokines transforming growth factor-beta 1 (Corrin *et al.* 1994) and tumor

22   necrosis factor alpha (Rolfe *et al.* 1992) in lung cells. Potolicchio *et al.* (1997) reported a

23   strong genetic association between hard-metal disease and the presence of a glutamate

24   residue at position 69 of the HLA-DP [MHC II antigen] molecule. In a later publication,

25   Potolicchio *et al.* (1999) demonstrated that HLA-DP but not HLA-DR could bind cobalt

26   *in vitro*, which they suggested could be a possible explanation for this genetic association

27   with hard-metal disease.

28   *Extrarespiratory effects*

29   Memory loss has been reported and studied in patients diagnosed with hard-metal disease

30   (Jordan *et al.* 1990, Jordan *et al.* 1997, Jordan *et al.* 1993). In one study (Jordan *et al.*

1   1990, 1993), 12 former tungsten carbide workers who had complained of memory loss

2   were compared with 26 healthy, unexposed adults matched for sex, age, race, and

3   education. All subjects were administered the Wechsler Memory Scale-Revised (WMS-

4   R), the Peterson Word Triad, and Squire's Television Title Recognition Tests. The test

5   groups were found to have significantly lower verbal memory ($P < 0.001$) and attention

6   ($P < 0.01$) scores, but no differences in visual-spatial memory. It was noted by the

7   authors that exposures to mixed solvents by the patients with hard-metal disease was a

8   potentially confounding factor. In a second study (Jordan *et al* 1997), exposure to mixed

9   solvents was controlled for by including a group with exposure to mixed solvents but no

10   hard-metal exposures. Memory tests were administered for a range of functions:

11   attention, short-term, delayed, and remote verbal and visual memory. Both groups

12   exhibited memory deficits compared with unexposed controls on tests of verbal memory

13   and attention. The authors acknowledged the evidence for independent effects of

14   exposure to hard metals on memory over exposure to solvents alone was inconclusive.

15   However, when the authors selected for more closely matched groups, hard-metal

16   workers had memory deficits greater than those attributable to solvent exposure alone.

17   Cobalt is cardiotoxic, and there is conflicting evidence that industrial exposure to cobalt

18   can cause cardiomyopathy (IARC 2006). Horowitz *et al.* (1988) found that cobalt

19   exposure was associated with adverse effects on ventricular function among cemented-

20   tungsten carbide workers. Hogstedt and Alexandersson (1990) reported an increased risk

21   (border line significance) of death from ischemic heart disease among hard-metal

22   workers in the high-exposure group who were exposed for at least 10 years; however, no

23   excess mortality from ischemic heart disease was found in the studies of French hard-

24   metal workers (Moulin *et al.* 1998, Wild *et al.* 2000, Lasfargues *et al.* 1994).

25   Lechleitner *et al.* (1993) reported a case of Goodpasture's syndrome in a 26-year-old man

26   who had worked in a metallurgical plant processing hard metals for three years. The

27   patient presented with fever and dyspnea. High amounts of tungsten, but no cobalt, were

28   detected in granular inclusions contained in alveolar macrophages. The authors

29   concluded that although a causative role of hard-metal exposure and the development of

30   Goodpature's syndrome could not be proved conclusively, the case did illustrate the

1   potential complex interrelations among autoimmune disease, immune defects, and

2   exposure to substances with possible antigenic properties.

3   5.2.2   *Animal models of hard-metal toxicity*

4   Rats exposed to hard-metal particles developed some features of hard-metal disease,

5   particularly alveolitis and fibrosis, in some, but not all, studies. However, Nemery and

6   Hoet (2000) reported that multinucleated giant cells, which they identified as the most

7   characteristic feature of hard-metal lung disease, have not been observed in any animal

8   studies. The effects of hard metals in the lung of experimental animals are summarized

9   below.

10   Kitamura *et al.* (1980) exposed male Sprague-Dawley rats to a single dose of 23 mg/100

11   g b.w. of cemented tungsten carbide dust (presintered hard-metal ground with a diamond

12   wheel and administered intratracheally). Approximately 20% of the animals died within

13   three days after exposure, and the lungs showed hemorrhagic edema with intense alveolar

14   congestion. Surviving animals were killed at six months and twelve months. All animals

15   killed at six months had pulmonary lesions of patchy fibrosis in the vicinity of deposited

16   dust, but no definitive inflammatory reaction or interstitial pneumonitis (alveolitis) was

17   found. At twelve months one-third of the animals continued to show similar effects in the

18   lung while the remaining two-thirds had neither fibrosis nor dust deposits, showing

19   regression of the lesions.

20   Lasfargues and coworkers studied the acute (Lasfargues *et al.* 1992) and delayed

21   (Lasfargues *et al.* 1995) responses of female Sprague-Dawley rats to pure cobalt metal

22   powder and cobalt–tungsten carbide powder (see Section 5.2.3 and Table 5-1 for acute

23   cytotoxic effects). Intratracheal instillation of 1.0 mg cobalt/100 g b.w. resulted in 20%

24   mortality within 24 hours but no marked changes in lung histology. The dose of 16.67 mg

25   cobalt–tungsten carbide (equivalent to 1.0 mg cobalt)/100 g b.w. resulted in 60%

26   mortality, and lung histology in these animals showed an acute and diffuse inflammatory

27   reaction with generalized edematous alveolitis.

28   Adamis *et al.* (1997) compared the lung toxicity of samples of respirable cobalt–tungsten

29   carbide obtained at three stages of the manufacturing process in a hard-metal producing

1   plant: as finished powder for pressing (FP); from a heat-treated, pre-sintered sample

2   obtained at 800°C (PH), and from wet grinding of sintered hard metal obtained by heat

3   treatment at 1,200°C (HM). Rats were killed for bronchoalveolar lavage (biochemical

4   studies for cytotoxicity endpoints are summarized in Table 5-1) and histological studies

5   at 1, 4, 7, and 30 days after treatment. Histological examination of the lungs showed

6   fibrosing alveolitis that developed by 30 days with all three sample types.

7   5.2.3   *Cytotoxicity studies*

8   Table 5-1 summarizes the study methods and results of *in vitro* and *in vivo* studies

9   evaluating the cytotoxicity of cobalt–tungsten carbide. Two *in vivo* studies (intratracheal

10 administration) showed greater toxic effects with cobalt–tungsten carbide than with

11 cobalt powder alone in the lungs of female Sprague-Dawley rats (Huaux *et al.* 1995,

12 Lasfargues *et al.* 1995), Cytotoxicity was measured by cell number, lactate

13 dehydrogenase (LDH), total protein, *N*-acetyl-β-ᴅ-glucosaminidase (NAG) or albumin.

14 Adamis *et al.* (1997) determined the cytotoxicity of respirable samples collected at

15 different stages of the hard-metal manufacturing process. They tested finished powder for

16 pressing (8% cobalt); heat-treated, pre-sintered material (8% cobalt); and powder

17 resulting from wet grinding of sintered hard metals (3% cobalt). Pathological changes

18 were seen in histological sections of the lungs with all three materials. The degree of lung

19 toxicity varied among the three powders, with the pre-sintered material being the most

20 toxic.

21 Similar to the *in vivo* studies*, in vitro* studies using mouse peritoneal macrophages (Lison

22 and Lauwerys 1990, 1992, 1994), rat alveolar macrophages (Lison and Lauwerys 1990,

23 Roesems *et al.* 1997, Roesems *et al.* 2000), and rat type II pneumocytes (Roesems *et al.*

24 1997, Roesems *et al.* 2000) have also shown greater toxic effects with cobalt–tungsten

25 carbide than with cobalt powder alone. (Study details are described in Table 5-1). No

26 toxicity (as assessed by LDH release) was observed for either cobalt, tungsten, or cobalt–

27 tungsten carbide in human type II pneumocytes (Roesems *et al.* 1997) or in another study

28 of rat alveolar macrophages when toxicity was assessed by release of IL-1, tumor

29 necrosis factor-α (TNF-α), fibronectin, or cystatin-C (Huaux *et al.* 1995)

1 [Although it often is assumed that the toxicity of metallic compounds is mediated by their

2 solubilized ions, there is evidence that the toxic effects of hard-metal particles result, at

3 least in part, from a surface-chemistry reaction occurring at the particulate level.] The *in*

4 *vitro* toxicity of cobalt–tungsten carbide particles was greater than cobalt alone, but the

5 synergistic effect was only observed when the cobalt and tungsten particles were in direct

6 contact with cells (Lison and Lauwerys 1992, Roesems *et al.* 2000). Although cobalt

7 solubilization was increased in the presence of tungsten carbide, the increased

8 bioavailability of cobalt alone did not account for the greater toxicity of the mixture. The

9 uptake of cobalt by mouse peritoneal macrophages was greater when the metal was in the

10 form of hard-metal particles. However, the *in vitro* toxicity of hard-metal particles to

11 mouse peritoneal macrophages was greater than cobalt alone even at equivalent

12 intracellular cobalt concentrations (Lison and Lauwerys 1994). Several *in vitro* and *in*

13 *vivo* experiments have demonstrated that a specific toxic reaction results from the

14 interaction between cobalt metal and tungsten carbide particles and oxygen to produce

15 reactive oxygen species. Thus, hard-metal dust behaves as a specific toxic entity (Lison

16 and Lauwerys 1992).

17 Roesems *et al.* (2000) reported that the cytotoxic action of cobalt or cobalt–tungsten

18 carbide could be reproduced partly or totally by treating the cells with leachate from these

19 particles. Furthermore, cobalt chloride was also cytotoxic to rat lung cells. Based on these

20 findings, the authors concluded that cobalt ions play a role in the toxicity of cobalt–

21 tungsten carbide particles as well as cobalt particles. In contrast, Lison and Lauwerys

22 (1992) reported that cobalt chloride was not cytotoxic to mouse peritoneal macrophages

23 and that solubilization of cobalt from the mixture was not a critical factor. Lison (2000)

24 suggested that the difference in results was most likely due to the presence of protein

25 (lactalbumin hydrolysate), which would bind the free cobalt ions, in the culture medium

26 used in the studies by Lison and Lauwerys (1990, 1992). Lison (2000) believed that the

27 cytotoxic action of cobalt ions in the absence of proteins was of limited biological

28 relevance and that the toxicity of cobalt–tungsten carbide particles was independent of

29 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 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.) Co (0.06 mg/100 g b.w.) 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 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.) Co (0.06, 0.3, and 0.6 mg/100 g b.w.) 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.
Male Sprague-Dawley rats 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): 1) finished powder for pressing[c] (FP) 2) heat-treated, pre-sintered sample obtained at 800°C[c] (PH) 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: PH > HM > FP 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. 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. 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 Lison and Lauwerys 1992	LDH release	CoWC[a] (100 µg/mL) Co (6 µg/mL) 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	LDH release	CoWC[a] (50 or 150 µg/mL)	CoWC produced a greater toxic effect (increased LDH release) than Co alone

Test system (reference)	Endpoint(s)	Test agent	Results
macrophages Lison and Lauwerys 1994		Co (3, 9, or 20 μg/mL)	even when the intracellular concentration of cobalt was the same.
Mouse peritoneal macrophages Lison and Lauwerys 1990	LDH release, morphology	CoWC[a] Co WC 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 alveolar macrophages Huaux et al. 1995	release of interleukin-1 (IL-1), TNF-α, fibronectin, and cystatin-c by lung phagocytes	CoWC[a] (50 μg/mL) Co (3 μg/mL) WC (50 μg/mL)	No significant effect on IL-1, TNF- α, fibronectin, or cystatin-c.
Rat alveolar macrophages Roesems et al. 1997	LDH release	CoWC[a] Co WC 0.118 to 1,180 μg/10^5 cells/200 μL/well for each powder	CoWC TD_{50} (per 10^5 cells) = 5 μg Co TD_{50} (per 10^5 cells) = 18 μg WC TD_{50} (per 10^5 cells) = 591 μg
Rat alveolar macrophages Roesems et al. 2000	MTT assay	CoWC[a] (83, 417, or 1,667 μg/700 μL/well) Co (5, 25, or 100 μg/700 μL/well)	CoWC doses 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 Lison and Lauwerys 1990	LDH release, morphology	CoWC[a] Co WC 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 Roesems et al. 1997	LDH release	CoWC[a] Co WC 0.118 to 1,180 μg/10^5 cells/200 μL/well for each powder	CoWC TD_{50} (per 10^5 cells) = 101 μg Co TD_{50} (per 10^5 cells) = 672 μg WC TD_{50} (per 10^5 cells) = 4,468 μg
Rat type II	MTT assay	CoWC[a] (83, 417, or 1,667	CoWC and Co showed similar toxicity

Test system (reference)	Endpoint(s)	Test agent	Results
pneumocytes Roesems *et al.* 2000		μg/700 μL/well) Co (5, 25, or 100 μg/700 μL/well)	
Human type II pneumocytes Roesems *et al.* 1997	LDH release	CoWC[a] Co WC 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; 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%.

1   5.2.4   *Biochemical studies of ROS formation*

2   Several lines of experimental evidence support a greater formation of ROS by the

3   combination of a mixture of cobalt and tungsten carbide particles compared with cobalt

4   metal particles alone. In a deoxyribose degradation assay to detect the capacity to

5   generate hydroxyl radicals *in vitro,* the activity of cobalt metal particles was significantly

6   increased (about threefold) by association with tungsten carbide particles (median

7   diameter = 2 μm) (Lison and Lauwerys 1993). Through the use of electron spin

8   resonance with a trapping reagent, it was shown that the production of hydroxyl radicals

9   by cobalt metal particles in aqueous buffered suspension was minimal, but the production

10   of free radicals was markedly increased in the presence of tungsten carbide particles (at a

11   ratio of 6% cobalt to 94% tungsten carbide); both a laboratory-prepared mixture and

12   powder from a hard-metal producing factory were tested (Lison *et al.* 1995). The ability

13   of cobalt metal particles to produce ROS was observed in the absence of hydrogen

14   peroxide and could not be fully reproduced with Co(II) ions, which Lison *et al.*

15   concluded was an indication that soluble cobalt ions were the product of the reaction

16   rather than its source, which would be typical of a Fenton-like mechanism. Kadiiska *et al.*

17   (1989) reported that for Co(II) in the presence of hydrogen peroxide, superoxide

1   formation predominated over production of hydroxyl radicals, and they also proposed

2   that Co(II) did not react with hydrogen peroxide by a classical Fenton reaction.

3   However, Mao *et al.* (1996) and Leonard *et al.* (1998) demonstrated that the ability of

4   Co(II) ions to generate ROS from hydrogen peroxide via a Fenton-like reaction could be

5   increased by biological chelators such as anserine, glutathione, and glycylglycylhistidine

6   and Mao *et al.* suggested that chelation in cellular systems could play a role in generation

7   of ROS by Co(II) in those systems. Lison and coworkers (Lison *et al.* 2001) subsequently

8   proposed that formation of ROS could result from either the interaction of cobalt metal

9   and tungsten carbide or from the Co(II) ions generated from the Fenton-like reaction of

10 the metal and carbide (see Section 5.4 and Figure 2-1).

11 Lison *et al.* (1995) also reported a significant ($P < 0.01$) increase in arachidonic acid

12 peroxidation in the presence of the cobalt and tungsten carbide mixtures compared with

13 either cobalt or tungsten carbide alone. When mouse peritoneal macrophages were

14 incubated with cobalt–tungsten carbide particles, the concentration of the mixture that

15 was toxic to 50% of the cells was increased threefold by the addition of BHT, an

16 antioxidant. Based on these experimental results, the authors proposed that production of

17 reactive oxygen species is mediated by contact between the cobalt and tungsten carbide

18 particles, which allows the rapid reduction of ambient oxygen; meanwhile, metallic

19 cobalt is simultaneously solubilized as Co(II). In this solid-solid interaction, molecular

20 oxygen is reduced at the surface of tungsten carbide particles through the flow of

21 electrons from the cobalt atoms to the oxygen molecules. The cobalt is consequently

22 oxidized to Co(II). Contrary to what happens in a Fenton-like reaction, Co(II) does not

23 drive the production of ROS, but is the product of this reaction (Figure 5-1).
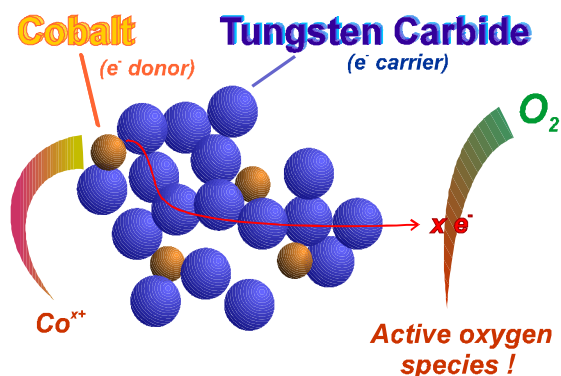
Lison et al. Chem. Res. Toxicol. 8 : 600-606 (1995)

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

1   Further investigations of the surface interaction between cobalt metal and tungsten

2   carbide particles prepared in the laboratory or obtained from a hard-metal production

3   factory (Zanetti and Fubini 1997) indicate that the two associated solids may act as a

4   distinct chemical entity. The authors concluded that the adsorption capacity and energy of

5   adsorption for water vapor and the catalytic decomposition of hydrogen peroxide, which

6   were higher than expected from the sum of the contributions by the two components,

7   could only be explained by a chemical reaction or activation occurring at the interface

8   between the components. Their joint presence thus provides a continual source of ROS.

9   In this reaction, cobalt is more active than other metals (e.g., iron or nickel) (Fenoglio *et*

10 *al.* 2000).

11 Keane *et al.* (2002) confirmed the generation of hydroxyl radicals by cobalt–tungsten

12 carbide hard metals in aqueous suspension by examining the properties of detonation

13 coating materials made of a mixture of cobalt and tungsten carbide (6.7% cobalt in the

14 starting material and 5.4% cobalt in the dust remaining after detonation coating; see

15 Section 2.4.4). The post-detonation material was a much stronger generator of hydroxyl

16 radicals than the pre-detonation material.

17 Francia *et al.* (2007) investigated the electrochemical process responsible for free radical

18 release in hard metals. They reported that the reaction can take place only when the

1   tungsten carbide surface is covered with a thin layer of electrolyte, a situation similar to

2   that encountered by cobalt–tungsten carbide particles in the distal parts of the lung. These

3   authors assembled a voltaic cell corresponding to the overall spontaneous electrochemical

4   process and demonstrated that cobalt in direct contact with tungsten carbide in an

5   electrolyte-wet environment spontaneously and rapidly oxidizes in relation to the oxygen

6   reduction catalyzed by tungsten carbide and that active oxygen species are produced.

7   [Overall, these experimental data indicate that the reaction of cobalt metal with ambient

8   molecular oxygen is amplified when the particles are associated with tungsten carbide,

9   i.e., in hard-metal particles.] Compared with cobalt metal alone, the rate of ROS

10   formation and hence of cobalt solubilization is markedly increased in the hard-metal

11   mixture. [It is well-known that both ROS and Co(II) ions can affect DNA integrity, and it

12   is therefore likely that both are involved in the mechanisms of genotoxicity of cobalt–

13   tungsten carbide (Lison *et al.* 2001).] ROS are involved directly or indirectly (e.g., via a

14   lipoperoxidation process) in the clastogenic activity of cobalt–tungsten carbide hard

15   metals (Lison *et al.* 2001). Genotoxic effects are discussed below in Section 5.3.

16   **5.3   Genetic damage and related effects**

17   Genotoxicity tests have been conducted with hard-metal particles *in vitro* and either

18   isolated human blood lymphocytes or isolated mouse DNA. The potential genotoxic

19   effect of hard-metal particles also has been examined *in vivo* in the lung of rats after

20   intratracheal administration. A single study examined a variety of genotoxicity

21   biomarkers in workers from the hard-metal industry in Europe. The results obtained with

22   hard-metal particles in these studies are summarized in Table 5-2 and reviewed below.

23   Mechanisms of the genotoxicity of cobalt–tungsten carbide hard-metal particles are

24   discussed in Section 5.4 and the genotoxicity of soluble cobalt compounds is summarized

25   in Section 5.5.

26   IARC reviewed the mutagenic effects of cobalt–tungsten carbide hard metals and cobalt

27   compounds in October 2003 and concluded that when cobalt metal particles are mixed

28   with tungsten carbide, a unique chemical entity is formed that produces higher amounts

29   of ROS than cobalt alone, is more mutagenic *in vitro* in human cells than cobalt alone,

30   and is mutagenic *in vivo* in rat lung cells (IARC 2006).

1 ### 5.3.1 *Prokaryotic and non-mammalian systems*

2 No studies on the potential genotoxicity of hard-metal particles in bacteria, yeast, or

3 insects were identified.

4 ### 5.3.2 *Mammalian systems* in vitro

5 The clastogenic activity of a cobalt–tungsten carbide particle suspension was evaluated

6 by measurement of DNA breaks and alkali-labile sites in the alkaline elution assay and by

7 alkaline single-cell gel electrophoresis (the comet assay). Alkaline elution measures the

8 rate of DNA elution through a filter membrane. An increase in the elution rate indicates

9 DNA damage (single-strand breaks, or lesions converted to single-strand breaks under

10 alkaline conditions) (Anard *et al.* 1997). The comet assay uses electrophoresis at a high

11 pH that results in migration of cellular DNA towards the anode. The appearance of a

12 comet is formed when the DNA contains single-strand breaks, or lesions converted to

13 single-strand breaks under alkaline conditions. The extent of DNA damage is determined

14 by the product of comet tail length and staining intensity. All of the cobalt–tungsten

15 carbide used in these studies was laboratory prepared except the Anard *et al.* (1997)

16 study, which used presintered cobalt–tungsten carbide powder. When tested in concurrent

17 assays over a range of cobalt-equivalent concentrations, a mixture of cobalt and tungsten

18 carbide (6% and 94% by weight, respectively) caused on average three times as many

19 DNA breaks than cobalt metal particles alone, both in isolated mouse DNA (Anard *et al.*

20 1997) and in cultured human lymphocytes (Anard *et al.* 1997, De Boeck *et al.* 1998, Van

21 Goethem *et al.* 1997). Dose- and time-dependency of DNA breakage and alkali-labile

22 sites were characterized with the comet assay; significant DNA damage (increased

23 percentage of tail DNA) was noted after a 15-minute incubation with cobalt–tungsten

24 carbide particles at a concentration of 10 μg/mL (De Boeck *et al.* 1998). In the alkaline

25 elution assay, the DNA strand-breaking activity of cobalt–tungsten carbide particles was

26 inhibited in part by scavenging of ROS with formate (1 M) (Anard *et al.* 1997). However,

27 the comet assay did not detect a significant increase in oxidatively damaged DNA as

28 measured by formamidopyrimidine DNA glycosylase (Fpg)–sensitive sites, suggesting

29 the formation of DNA adducts (e.g., related to lipid peroxidation products) rather than

30 direct DNA oxidation by ROS (De Boeck *et al.* 1998). In concurrent assays, cobalt

31 chloride (at a concentration of up to 1 mM) and cobalt metal particles alone produced

1   significantly fewer DNA breaks or alkali-labile sites, and tungsten carbide alone was

2   completely inactive (Anard *et al.* 1997, De Boeck *et al.* 1998), indicating that the cobalt–

3   tungsten carbide mixture is a distinct genotoxicant.

4   A cobalt–tungsten carbide mixture also was more genotoxic than cobalt metal particles in

5   the micronucleus assay in cytokinesis-blocked human lymphocytes *in vitro* (De Boeck *et*

6   *al.* 2003a, Van Goethem *et al.* 1997). The lowest effective dose was the same for both

7   materials test, but overall the cobalt–tungsten carbide mixture had a stronger effect in

8   both studies; Van Goethem *et al.* described it as significantly enhanced while De Boeck

9   *et al.* reported that it was more pronounced but not statistically significant. Increased

10 rates of micronucleus formation may reflect either clastogenic or aneugenic events. The

11 aneugenic activity probably is mediated by Co(II) ions, because, unlike DNA breaks, it

12 also results from exposure to $CoCl_2$ (De Boeck *et al.* 1998). Two different mechanisms

13 for the genotoxicity of cobalt–tungsten carbide particles have been proposed: (1)

14 clastogenic effects mediated by ROS produced at the surface of these particles and (2)

15 aneugenic effects mediated by Co(II) ions released from these particles (see Section 5.4

16 for further discussion of mechanisms).

17 More recently, this *in vitro* genotoxicity has been found with mixtures of cobalt metal

18 with niobium carbide and chromium carbide; although these carbides alone did not

19 induce micronucleus formation in human lymphocytes, cobalt alone and, to a greater

20 extent, the carbide-cobalt mixtures induced a statistically significant concentration-

21 dependent increase in micronucleated binucleated cells. Molybdenum carbide (Mo_2C)

22 particles, which have a much smaller specific surface area than niobium or chromium

23 carbide particles, did not interact with cobalt particles in this test, consistent with the

24 hypothesis that the genotoxic effect results, at least in part, from a surface-chemistry

25 reaction (De Boeck *et al.* 2003a).

26 5.3.3   *Rat* in vivo *systems*

27 A single intratracheal instillation of cobalt–tungsten carbide particles administered to

28 male Wistar rats caused DNA strand breaks and alkali-labile sites (in the comet assay)

29 and micronucleus formation in rat type II pneumocytes, in a dose- and time-dependent

30 manner (De Boeck *et al.* 2003b). At a dose that caused mild pulmonary toxicity (16.6

1   mg/kg b.w.), cobalt–tungsten carbide particles significantly increased the percentage of

2   tail DNA (at 12 hours) and the frequency of micronuclei (at 72 hours). The authors

3   discussed two possible mechanisms to account for these genotoxic effects: the direct

4   mutagenic activity of cobalt–tungsten carbide particles (as demonstrated *in vitro*) and the

5   production of ROS by inflammatory cells recruited in the lung. In rat peripheral blood

6   mononucleated cells, no increase in DNA damage or micronuclei was observed,

7   indicating that circulating lymphocytes are poor reporter cells for monitoring the

8   genotoxic effects of inhaled particles. Bronchoalveolar lavage (BAL) cells of treated

9   animals showed statistically significantly lower levels of DNA migration than controls.

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] Co	DNA damage[d]	0.5 µg 1 µg	+ +	Anard *et al.* 1997
Human isolated peripheral blood lymphocytes	CoWC Co WC	DNA damage[d]	1.5 µg 3.0 µg 250 µg	+ + −	Anard *et al.* 1997
	CoWC Co WC	DNA damage[e]	3 µg 4.5 µg 100 µg	+ + −	
	CoWC Co WC	DNA damage[e]	0.6 µg[f] 0.6 µg 10 µg	+ + +	Van Goethem *et al.* 1997
	CoWC Co	DNA damage[e]	0.6 µg[f] 0.3 µg	+ +	De Boeck *et al.* 1998
	CoWC	Fpg-sensitive[e] sites	6 µg	−	
	CoWC CoNbC CoCr$_3$C$_2$ CoMo$_2$C Co WC	DNA damage[e]	0.6 µg 6 µg 0.6 µg 0.6 µg 0.6 µg 100 µg	+ + + + + −	De Boeck *et al.* 2003a
	CoWC Co WC	micronuclei in cytokinesis-blocked cells	0.6 µg[f] 0.6 µg 50 µg	+ + +	Van Goethem *et al.* 1997

Test system	Particle[a,b]	End point	LED/HID (Co eq/mL)	Result	Reference
	CoWC	micronuclei in cytokinesis-blocked cells	0.6 µg	+	De Boeck *et al.* 2003a
	CoNbC		3 µg	+	
	CoCr$_3$C$_2$		3 µg	+	
	CoMo$_2$C		6 µg	–	
	Co		3 µg	+	
	WC		50 µg	+	
In vivo **(Male Wistar rat-intratracheal instillation)**					
type II pneumocytes	CoWC	DNA damage[e] Micronuclei	16.6 mg/kg 16.6 mg/kg	+ +	De Boeck *et al.* 2003b
peripheral-blood lymphocytes	CoWC	DNA damage[e] Micronuclei	16.6 mg/kg 49.8 mg/kg	– –	
BAL	CoWC	DNA damage[e]	16.6 mg/kg	–	

BAL = broncho-alveolar lavage cells; Co = cobalt; CoWC = cobalt–tungsten carbide; Co eq/mL = cobalt equivalent concentration for *in vitro* studies; Cr$_3$C$_2$ = chromium carbide; Fpg =formamidopyrimidine DNA glycosylase (measures oxidative damage); HID = highest ineffective dose; LED = lowest effective dose; Mo$_2$C = 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.

1   5.3.4   *Human exposure* in vivo

2   The possible genotoxic effects of occupational exposure to hard-metal dust (cobalt–

3   tungsten carbide) at the TLV-TWA limit for cobalt-containing dust (20 µg/m^3) was

4   explored in a study using several end points (De Boeck *et al.* 2000). The study examined

5   three groups of male workers: 35 workers (mean age = 38.5 ± 7.7 [SD] years, range =

6   27.7 to 55.3) exposed to cobalt dust from three refineries, 29 workers (mean age = 40.7 ±

7   12.4 years, range = 20.7 to 63.6) exposed to hard-metal particles from two hard-metal

8   production plants, and 27 matched control subjects (mean age = 38.0 ± 8.8 years, range =

9   23.3 to 56.4) recruited from the administrative departments of the respective plants.

10 Smoking habits were identical in the three groups. The geometric mean levels of urinary

11 cobalt (expressed as micrograms of cobalt per gram of creatinine) were consistent with an

12 average exposure at the TLV-TWA in cobalt workers (21.5 µg/g, range = 5.0 to 82.5) and

13 hard-metal workers (19.9 µg/g, range = 4.0 to 129.9) and the absence of occupational

14 exposure in controls (1.7 µg/g, range = 0.6 to 5.5).

1   The study design integrated complementary biomarkers of DNA damage: 8-

2   hydroxydeoxyguanosine (8-OHdG) in urine, DNA single-strand breaks and Fpg-sensitive

3   sites (used to detect oxidative damage to DNA; see Glossary for definition) in the comet

4   assay, and the *in vitro* cytochalasin-B micronucleus test in blood lymphocytes.

5   Micronuclei were scored both in binucleated and in mononucleated cells, to discriminate

6   between micronuclei accumulated *in vivo* (mononucleates) and additional micronuclei

7   expressed *in vitro* (binucleates). The results of biomarkers for genotoxicity did not differ

8   significantly between controls and workers exposed to cobalt-containing dust or between

9   workers exposed to cobalt-containing dust and hard-metal dust. The only significant

10 difference observed was a higher frequency of micronuclei in cytokinesis-blocked

11 lymphocytes in workers exposed to cobalt than in workers exposed to hard-metal dust.

12 However, the frequencies did not differ significantly from those for the exposed workers'

13 concurrent controls. Multiple regression analysis indicated that workers who smoked and

14 were exposed to hard-metal dusts had significantly elevated 8-OHdG and micronucleus

15 values. [The power to detect effects was limited by the small sample size and the use of

16 blood lymphocytes, which are poorly sensitive reporter cells. Strengths of the study were

17 that the workers were matched for smoking and drinking habits and came from more than

18 one plant.]

19 Mateuca *et al.* (2005) followed up the *in vivo* genotoxicity study by De Boeck *et al.*

20 (2000) of workers exposed to cobalt and hard-metal dusts and examined the influence of

21 DNA repair enzyme polymorphisms on the genotoxicity endpoints. In the total

22 population (exposed and controls), multiple regression analyses found that DNA strand

23 breaks (as detected by the comet assay), binucleate micronuclei frequency, and 8-OHdG

24 were all associated with the interaction between smoking and exposure. In addition, DNA

25 strand breaks were influenced by the type of plant (higher among exposed workers from

26 cobalt–tungsten carbide plants than workers from cobalt plants), and XRCC1 (X-ray-

27 cross complementing group) polymorphisms and binucleate micronucleus frequency also

28 were influenced by the type of plant (higher among workers from cobalt plants).

29 Mononucleate micronuclei were associated with being a smoker and working in a cobalt–

30 tungsten carbide plant and having variant genotypes for both XRCC3 and hOGG1 (8-

31 oxo-guanine-DNA glycosylase/AP lyase). In the exposed population, XRCC3 and

1   XRCC1 genotypes were related to single-strand breaks and the presence of variants for

2   both hOGG1 and XRCC3 was related to micronuclei frequency (mononucleates). In

3   addition, the interaction between the type of plant and smoking status influenced

4   micronuclei and 8-OHdG. While the authors felt that the strength of the study lay in

5   genotyping combined with several genotoxicity parameters, they noted that the limited

6   number of subjects was a relative weakness.

7   **5.4   Mechanistic studies and considerations**

8   The mechanism by which exposure to hard metals might induce cancer is not completely

9   understood, but Lombaert *et al.* (2008) concluded that the available data indicate that

10   simultaneous exposure to cobalt metal and tungsten carbide particles is required to exert

11   genotoxic effects, which might be an important factor in the potential carcinogenicity of

12   hard metals.

13   Lison *et al.* (2001) reviewed the evidence comparing the genotoxicity of cobalt

14   compounds and cobalt–tungsten carbide hard metals from their studies and those of other

15   investigators. Hard-metal (cobalt–tungsten carbide) particles caused significantly more

16   (approximately threefold) DNA breaks than were detected with cobalt metal particles

17   alone for both isolated human DNA and cultured human lymphocytes by the alkaline gel

18   electrophoresis (comet) assay. The genotoxic activity of cobalt–tungsten carbide also was

19   greater than that of cobalt metal particles in the cytokinesis-blocked micronucleus test in

20   human lymphocytes *in vitro;* confirming the unique toxicological properties of the

21   cobalt–tungsten carbide mixture that had initially been demonstrated in cell cytotoxicity

22   assays and animal experiments.

23   The genotoxic effects of cobalt–tungsten carbide particles has been proposed to result

24   from ROS produced at the solid-liquid interface (mainly clastogenicity) and from ionic

25   cobalt forms dissolved in biological media (possibly chromosome or genome mutations).

26   Lombaert *et al.* (2004) showed that cobalt–tungsten carbide particles induced apoptosis in

27   cultured human lymphocytes at a dose previously demonstrated to cause genotoxicity in

28   these cells. Although tungsten carbide had generally been considered to be biologically

29   inert, Lombaert *et al.* found that tungsten carbide particles in the absence of cobalt also

30   caused apoptosis in human lymphocytes. The induction or modulation of apoptosis by

1   Co(II) ions and other cobalt-containing compounds (reviewed by De Boeck *et al.* 2004)

2   might have some bearing on the mechanism of potential hard-metal carcinogenicity.

3   A number of mammalian genes (e.g., the genes for metallothionein, heat-shock proteins,

4   and the c-Fos protein) are transcriptionally regulated by a *cis*-acting DNA element in

5   their upstream regions that responds to various metals, including cobalt, to stimulate their

6   expression (Murata *et al.* 1999). These effects are observed *in vitro* at high cobalt

7   concentrations (> 10 μM), but it is unknown whether these phenomena might play a role

8   in pathophysiological processes involved in cobalt carcinogenesis. A similar mechanism

9   is involved in the ability of soluble cobalt (generally cobalt chloride) to induce several

10   tissues and cells to mimic the pathophysiological response to hypoxia (Beyersmann

11   2002). This response involves various genes, including those coding for erythropoiesis

12   and angiogenesis (Gleadle *et al.* 1995, Steinbrech *et al.* 2000).

13   Cobalt also interferes with cellular mechanisms that control the degradation of regulatory

14   proteins such as p53, which is involved in control of the cell cycle, genome maintenance,

15   and apoptosis. It has been reported that in mammalian cells, cobalt (at a concentration of

16   100 μM) activates hypoxia-inducible factor-1α, which in turn induces accumulation of

17   p53 through direct association of the two proteins (An *et al.* 1998). Inhibition of

18   proteasome activity in human alveolar macrophages by cobalt (at 100 μM), subsequent

19   accumulation of ubiquitinated proteins, and increased apoptosis have been reported

20   (Araya *et al.* 2002). Whether these biochemical mechanisms are involved in the

21   carcinogenicity observed with some cobalt compounds (including cobalt–tungsten

22   carbide powders and hard metals) remains, however, to be examined.

23   In studies designed to explore the molecular mechanisms of gene response to hypoxia,

24   cobalt (as cobalt chloride at a dose of 12 to 60 mg/kg b.w.) upregulated expression of

25   *PDGF-B* (platelet-derived growth factor-B) in lungs and kidneys of male Sprague-

26   Dawley rats (Bucher *et al.* 1996). Because PDGF is an important growth factor that

27   modulates cell proliferation and the expression of several proto-oncogenes, mainly in

28   mesenchymal cells, this effect of cobalt might explain its fibrogenicity and/or

29   carcinogenicity, but this remains to be documented.

1   Cobalt ions may mimic or replace other essential divalent metal ions (e.g., magnesium,

2   calcium, iron, copper, or zinc), thus altering many important cellular reactions and

3   functions (NTP 2002a). The ability of cobalt ions to inhibit DNA repair processes or

4   interact with hydrogen peroxide to form ROS may contribute to the genotoxic and

5   carcinogenic effects reported for cobalt sulfate and other cobalt compounds (Beyersmann

6   and Hartwig 1992, Lison *et al.* 2001) (Figure 5-2).
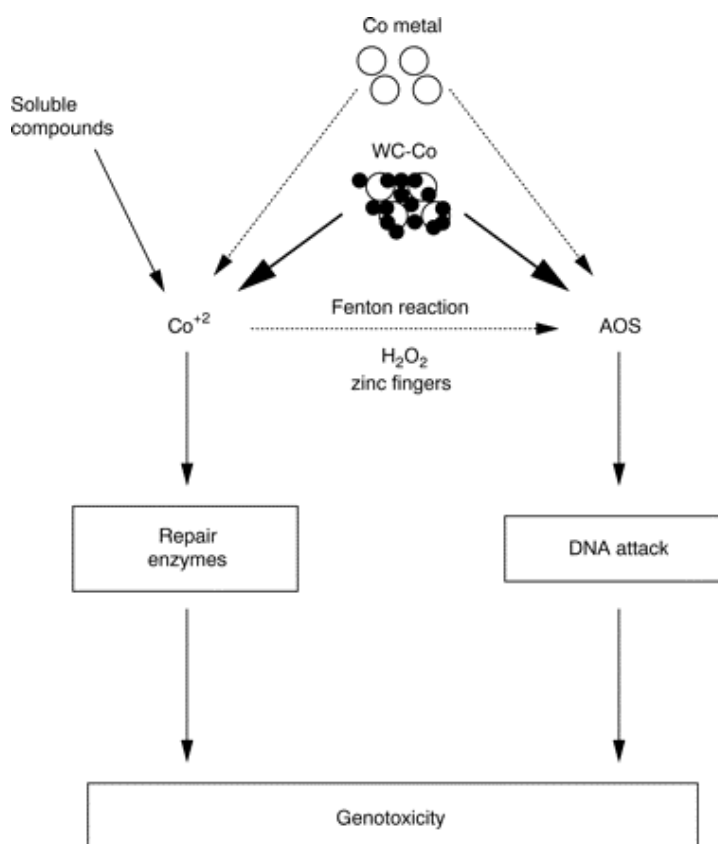
Figure 5-2. Mechanisms of genotoxicity of cobalt–tungsten carbide (CoWC) hard metal and cobalt

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

1 Lombaert *et al.* (2008) investigated the *in vitro* expression of genes responsive to hard-

2 metal exposure in human peripheral blood mononucleated cells (PBMC) and monocytes

3 isolated from PBMC. High-density microarrays were used to analyze gene expression

4 profiles after a 24-hour exposure. PBMC and monocytes were exposed in the same

5 medium to 6.0 μg/mL cobalt-equivalent doses of cobalt chloride, metallic cobalt,

6 tungsten carbide, or cobalt–tungsten carbide. Doses were selected based on levels that

7 were previously shown to induce genotoxic effects and apoptosis. The most significantly

8 up-regulated pathways in cobalt–tungsten carbide-treated PBMC included apoptosis

9 regulation and stress/defense response, and the most down-regulated pathway was

10 immune response. For monocytes, the most significantly up- and down-regulated

11 pathways were nucleosome/chromatin assembly and immune response, respectively.

12 Although these data did not identify the specific genes responsible for hard-metal–

13 induced effects, or explain its carcinogenic effects, the results indicated that a large

14 number of genes associated with cell biology and survival were affected. Furthermore,

15 the similarity of effect of cobalt alone compared with cobalt–tungsten carbide did not

16 indicate mechanisms involved in the unique carcinogenic activity of cobalt–tungsten

17 carbide. Rather, the authors concluded that the critical event was most likely the higher

18 oxidative burst released by cobalt–tungsten carbide compared with cobalt alone.

19 **5.5   Carcinogenicity, genotoxicity, and toxicity of cobalt compounds, cobalt metal**
20 **alloys, cobalt powder or dust, and tungsten carbide**

21 Because cobalt–tungsten carbide powders and hard metals contain cobalt particles and

22 release Co(II) ions, the information available on the potential genotoxicity and

23 carcinogenicity of cobalt metal and soluble cobalt compounds, including cobalt sulfate, is

24 relevant in evaluating the carcinogenicity of cobalt–tungsten carbide powders and hard

25 metals. IARC (2006) concluded that cobalt metal without tungsten carbide was *possibly*

26 *carcinogenic to humans* (Group 2B), and cobalt sulfate and other soluble cobalt (II) salts

27 were *possibly carcinogenic to humans* (Group 2B). Cobalt sulfate is listed in the *Report*

28 *on Carcinogens, Eleventh Edition* as *reasonably anticipated to be a human carcinogen,*

29 based on sufficient evidence in animals. An NTP background document reviewing the

30 evidence concerning the carcinogenicity of cobalt sulfate is available (NTP 2002a).

1 5.5.1 *Carcinogenicity of cobalt compounds in experimental animals*

2 The available studies on carcinogenicity of cobalt compounds other than cobalt–tungsten

3 carbide powders and hard metals in animals are summarized in Table 5-3. In a two-year

4 inhalation study conducted by NTP (1998), cobalt sulfate heptahydrate induced lung

5 tumors in mice and rats and adrenal tumors in female rats (Bucher *et al.* 1999). Other

6 soluble cobalt compounds (cobalt chloride and naphthenate) produced local tumors at

7 injection sites. No recent inhalation study of insoluble cobalt compounds was identified.

8 Early studies with cobalt oxides found local tumors at injection sites and lung tumors

9 after intratracheal instillation. Early studies with cobalt metal alone or in alloys found

10 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) 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 10 mg/kg	5 d/wk for 2 yr 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	intraarticular	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
	intraarticular	Fischer-344 rats (M)	8–12	20 mg	single injection, observed for 24 mo	NTR
wrought Vitallium[a] cast Vitallium[b] 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 Co-Mo Co-W Co-Zr 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%].

1   5.5.2   *Genotoxicity of cobalt compounds*

2   Like other metallic forms, Co(II) compounds are relatively inactive in prokaryotic

3   systems (Rossman 1981, Swierenga *et al.* 1987).

4   In mammalian cells, the results of the assays with soluble Co(II) salts clearly

5   demonstrated their mutagenic potential (reviewed by De Boeck *et al.* 2003c). Two

6   molecular mechanisms seem to apply: (1) a direct effect of Co(II) ions to damage DNA

7   through a Fenton-like mechanism (e.g. Mao *et al.* 1996) and (2) an indirect effect through

8   inhibition of the repair of DNA damage caused by endogenous events or other agents

9   (e.g. Kasten *et al.* 1997). The ability of Co(II) ions to compete with other species in the

10   zinc finger domains of proteins involved in cell-cycle control and/or DNA repair may

11   help to explain the latter effect of these cations (Hartwig *et al.* 2002).

12   These molecular mechanisms apply to soluble cobalt compounds, such as cobalt chloride

13   or sulfate, and also to cobalt metal and hard-metal particles, which are readily solubilized

14   in biological media. *In vivo*, however, the bioavailability of Co(II) is relatively limited,

15   because these cations precipitate in the presence of physiological concentrations of

16   phosphates ($K_{sp} = 2.5 \times 10^{-35}$ at 25°C) and bind to proteins such as albumin.

17   The genotoxicity data available for cobalt compounds other than cobalt–tungsten carbide

18   powders and hard metals are summarized in Table 5-4.

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

Cobalt compound	Test system	End point	Result	Reference
Prokaryotic				
cobalt chloride	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537, TA1538, TA2637	reverse mutation	–	Tso and Fung 1981, Ogawa *et al.* 1986, Mochizuki and Kada 1982, Arlauskas *et al.* 1985
cobalt chloride	*Bacillus subtilis* rec assay	growth inhibition	– + or weakly +	Nishioka 1975 Kanematsu *et al.* 1980

Cobalt compound	Test system	End point	Result	Reference
cobalt chloride	*Escherichia coli* reversion assay	reverse mutation	–	Kada and Kanematsu 1978, Arlauskas *et al.* 1985
cobalt chloride	*E. coli*	prophage induction	–	Rossman *et al.* 1984
cobalt sulfate	*S. typhimurium* TA98, TA1535 TA100	reverse mutation	– +	Zeiger *et al.* 1992
cobalt (III) complexes	*S. typhimurium* TA92, TA98, TA100	reverse mutation	+ (4 complexes)[a] – (11 complexes)[b]	Schultz *et al.* 1982
cobalt (III) complexes	*E. coli* repair assay	DNA damage	+ (4 complexes)[a] – (11 complexes)[b]	Schultz *et al.* 1982
cobalt (III) complexes	*B. subtilis* rec assay	growth inhibition	+	Kanematsu *et al.* 1980
cobalt carbonate–cobalt hydroxide (cobalt III)	*B. subtilis* rec assay	growth inhibition	+	Kanematsu *et al.* 1980
Yeast				
cobalt chloride	*Saccharomyces cerevisiae* (plate assay)	gene conversion or petite mutation	+ or weakly +	Egilsson *et al.* 1979, Fukunaga *et al.* 1982, Kharab and Singh 1985, 1987, Lindegren *et al.* 1958, Prazmo *et al.* 1975, Singh 1983
cobalt chloride	*S. cerevisiae* (plate assay)	gene mutation	–	Fukunaga *et al.* 1982, Putrament *et al.* 1977, Singh 1983
Mammalian *in vitro*				
cobalt chloride	Chinese hamster ovary (CHO) & V79 cells	DNA strand breaks or gene mutation	+ or weakly +	Hamilton-Koch *et al.* 1986, Hartwig *et al.* 1990, Miyaki *et al.* 1979
cobalt chloride	mouse macrophage P388D1 cells	sister chromatid exchange (SCE)	+	Andersen 1983
cobalt chloride	human lymphocytes and leukocytes	chromosomal aberrations	–	Olivero *et al.* 1995, Paton and Allison 1972
cobalt chloride	human lymphocytes	DNA damage	+	De Boeck *et al.* 1998

Cobalt compound	Test system	End point	Result	Reference
cobalt chloride	human lymphocytes, human white blood cells, human diploid fibroblasts	DNA strand breaks or DNA migration	+	De Boeck *et al.* 2003c, Hamilton-Koch *et al.* 1986, McLean *et al.* 1982
cobalt chloride	human lymphocytes	SCE	+	Andersen 1983
cobalt chloride	human lymphocytes	aneuploidy	+	De Boeck *et al.* 2003c
cobalt chloride	human HeLa cells	inhibition of DNA synthesis	+	Painter and Howard 1982
cobalt sulfate	Syrian hamster embryo (SHE) cells	cell transformation	+	Kerckaert *et al.* 1996a, Kerckaert *et al.* 1996b
cobalt sulfate	mouse fibroblast NCTC 929 cells	induction of tumor suppressor protein p53 cells	+	Duerksen-Hughes *et al.* 1999
cobalt sulfate	human lymphocytes	chromosomal aberrations	−	Olivero *et al.* 1995
cobalt sulfate	human lymphocytes	micronuclei	+	Olivero *et al.* 1995
cobalt sulfate	human c-Ha-*ras*-1-protooncogene DNA fragments	DNA damage	+ (with sodium sulfite)	Kawanishi *et al.* 1989
cobalt sulfate	human K562 cells	DNA damage	+ (with hydrogen peroxide)	Nackerdien *et al.* 1991
cobalt nitrate	human lymphocytes	chromosomal aberrations	−	Olivero *et al.* 1995
cobalt sulfide	CHO cells	DNA strand breaks	+	Robison *et al.* 1982
cobalt sulfide	SHE cells	cell transformation	+	Costa *et al.* 1982
cobalt acetate	CHO cells	DNA strand breaks	+	Robison *et al.* 1982
cobalt metal	human lymphocytes	DNA strand breaks	+	Anard *et al.* 1997
cobalt metal	human lymphocytes	DNA damage	+	De Boeck *et al.* 1998
cobalt metal	human osteosarcoma cells	micronuclei: CB micronucleus test / alkaline elution	+ / −	De Boeck *et al.* 2003c
cobalt metal	human lymphocytes	DNA breakage / micronuclei	+ (3 studies) − (1 study) / +	De Boeck *et al.* 2003c
cobalt molybdate	SHE cells	viral cell transformation	+	Casto *et al.* 1979

Cobalt compound	Test system	End point	Result	Reference
Mammalian *in vivo*				
cobalt chloride	Syrian hamster bone marrow and testes	aneuploidy	+	De Boeck *et al.* 2003c
cobalt chloride	mouse bone marrow	chromosomal aberrations	+	De Boeck *et al.* 2003c
cobalt acetate	rat kidney, liver, and lung	DNA base damage	+	De Boeck *et al.* 2003c

− = negative, + = positive, weakly + = weakly positive.
[a]*trans*-[Co(4-pic)$_4$Cl$_2$]Cl; *trans*-[Co(3-pic)$_4$Cl$_2$]Cl; *cis*-[Co(phen)$_2$Cl$_2$]Cl; *cis*-[Co(phen)$_2$ox]Cl.
[b][Co(NH$_3$)$_6$]Cl$_3$; (+)-[Co(en)$_3$]Cl$_3$; (+)[Co(en)$_3$]I$_3$; (+)-[Co(en)$_3$]I$_3$; [Co(pn)$_3$]Cl$_3$; [Co(en)$_2$ox]Cl; (−)-[Co(en)$_2$ox]Cl; *cis*-[Co(en)$_2$Cl$_2$]Cl; trans-[Co(en)$_2$Cl$_2$]Cl; trans-[Co(pyr)$_4$Cl$_2$]Cl; *cis*-[Co(bipy)$_2$Cl$_2$]Cl.

1   5.5.3   *Toxicity of cobalt compounds or tungsten carbide*

2   The health effects reported for exposure to cobalt (as part of various individual cobalt

3   compounds) include respiratory toxicity, skin allergy, goiter and reduced thyroid activity,

4   cardiotoxicity, polycythemia, and reproductive effects (for more information, see review

5   by Barceloux 1999). In occupational settings, the respiratory effects are the main health

6   effects of concern. These effects consist of upper airway irritation, bronchial asthma,

7   fibrosing alveolitis, and possibly lung cancer. Fibrosing alveolitis occurs almost

8   exclusively in a small fraction of workers employed in hard-metal producing facilities

9   (Lison *et al.* 1996) (see Section 5.2.1).

10   No information is available on the health effects of exposure to tungsten carbide.

11   However, several studies (Sahle 1992, Sahle *et al.* 1996, Sahle *et al.* 1994) suggest that a

12   potential toxic effect of tungsten oxide fibers (whiskers) on the lungs of exposed workers

13   should be investigated, based on reports that tungsten oxide fibers are cytotoxic to human

14   lung cells and on the hypothesis that oxygen free radicals are involved in the toxicity of

15   mineral fibers.

16   5.5.4   *Carcinogenicity and other studies of a tungsten-cobalt alloy*

17   Kalinich *et al.* (2005) reported that male Fischer 344 rats implanted intramuscularly (hind

18   legs) with tungsten alloy pellets (91.1% tungsten, 6.0% nickel, and 2.9% cobalt)

19   developed high-grade pleomorphic rhabdomyosarcomas at the site of implantation. These

20   tumors, which metastasized rapidly to the lung, developed in all rats (N = 46) implanted

21   with 20 tungsten alloy pellets (high dose) and in all rats (N = 46) implanted with 4

1   tungsten alloy pellets plus 16 titanium pellets (low dose) divided evenly between the hind

2   legs. Rats (N = 36) implanted with 20 nickel pellets as a positive control also developed

3   tumors, but the tumors developed at a slower rate than those in the tungsten alloy-

4   implanted rats. Rats (N = 46) in a negative control group implanted with 20 tantalum

5   pellets did not develop tumors.

6   Miller *et al.* (2001) had previously demonstrated that a mixture of tungsten, nickel, and

7   cobalt particles in similar proportions (92% tungsten, 5% nickel, and 3% cobalt) to those

8   of the tungsten alloy implants resulted in approximately nine-fold increases in

9   transformation frequency, approximately three-fold increases ($P < 0.01$) in induction of

10 micronuclei, and 8.5- to 9-fold ($P < 0.001$) increases in the number of DNA single-strand

11 breaks in human osteosarcoma (HOS) cells. Interestingly, the authors also demonstrated

12 that a mixture of tungsten (92%), nickel (5%), and iron particles (3%) tested in the same

13 system produced very similar results for the cell transformation and genotoxicity

14 endpoints.

15 **5.6   Summary**

16 5.6.1   *Absorption, distribution, metabolism, and excretion*

17 Humans are exposed to cobalt–tungsten carbide hard-metal particles through inhalation

18 and dermal contact. Hard-metal particles usually are of respirable size, suggesting that

19 they potentially are deposited throughout the respiratory tract, including in the alveoli.

20 Studies in humans and animals have demonstrated that when cobalt–tungsten carbide

21 hard-metal particles are deposited in the lung, cobalt metal is rapidly solubilized, cleared

22 from the lung, distributed in the body, and excreted in urine, whereas tungsten carbide

23 particles persist longer in lung tissue. Biomonitoring studies have detected cobalt and

24 tungsten in the urine of workers exposed to cobalt–tungsten carbide powders and hard

25 metal. Cobalt and tungsten also have been detected in whole blood, pubic hair, and

26 toenails, and tungsten has been detected in the feces of hard-metal workers.

27 5.6.2   *Toxicity*

28 Cobalt–tungsten carbide hard-metal dust has been shown to be more toxic than pure

29 cobalt or tungsten carbide in the lungs of rats and *in vitro* in rodent cells (mouse

1   peritoneal macrophages and rat alveolar macrophages) and human cells (type II

2   pneumocytes). Occupational inhalation exposure to cobalt–tungsten carbide hard-metal

3   dust is associated in some workers with the occurrence of hard-metal disease, a giant-cell

4   interstitial pneumonia that can develop into pulmonary fibrosis, with a potentially fatal

5   outcome. Other toxic effects reported in hard-metal workers included contact dermatitis,

6   occupational asthma, and memory loss.

7   5.6.3   *Genetic damage and related effects*

8   Cobalt–tungsten carbide genotoxicity and toxicity may be mediated both by solubilized

9   cobalt ions and through a surface chemistry reaction occurring at the particulate level.

10 Several *in vitro* and *in vivo* studies have demonstrated that a specific reaction results from

11 the interaction between cobalt metal and tungsten carbide particles and oxygen to

12 produce ROS. ROS are involved directly or indirectly (e.g., via a lipoperoxidation

13 process) in the genotoxicity of cobalt–tungsten carbide powders and hard metals.

14 Genotoxicity studies have demonstrated that cobalt–tungsten carbide hard metals cause

15 DNA damage and micronucleus formation in human peripheral blood lymphocytes *in*

16 *vitro* and in type II pneumocytes (but not peripheral blood lymphocytes) of rats exposed

17 *in vivo*. A study evaluating the genotoxic effects of occupational exposure to cobalt–

18 tungsten carbide hard-metal particles did not find increased DNA damage or

19 micronucleus formation in blood lymphocytes of exposed workers.

20 5.6.4   *Mechanistic studies and considerations*

21 Cobalt–tungsten carbide hard-metal particles caused significantly more (approximately

22 threefold increased) DNA breaks and micronuclei in cultured human lymphocytes than

23 cobalt particles alone, confirming that the cobalt–tungsten carbide mixture has unique

24 toxicological properties. The genotoxicity of cobalt–tungsten carbide particles has been

25 proposed to result from ROS produced at the solid-liquid interface, from ionic cobalt

26 forms dissolved in biological media, or from a combination of both mechanisms.

27 Potential mechanisms for cobalt–tungsten carbide hard-metal carcinogenicity may

28 involve the release of cobalt ions. Cobalt ions contribute to aneugenic effects (as evident

29 from micronucleus formation) and inhibit DNA repair processes. Cobalt ions also have

30 been shown to modulate apoptosis, regulate genes involved in the response to hypoxia,

1   and replace or mimic essential divalent metal ions in proteins regulating cell-cycle

2   control and DNA repair, thus altering cellular reactions.

3   5.6.5   *Carcinogenicity, genotoxicity, and toxicity of cobalt compounds, cobalt metal*
4   *alloys, cobalt powder or dust, and tungsten carbide*

5   Like other metallic forms, Co(II) compounds are relatively inactive in prokaryotic

6   systems, but genotoxic effects in mammalian cells have been proposed to involve either

7   direct DNA damage through a Fenton-like mechanism with Co(II) ions or an indirect

8   effect through inhibition of repair of DNA damage. The main health effects of concern

9   for hard metals in an occupational setting are respiratory effects, particularly fibrosing

10   alveolitis, but other toxic effects of cobalt include skin allergy, reduced thyroid activity,

11   cardiotoxicity, polycythemia, and reproductive effects. Several cobalt compounds (cobalt

12   sulfate, cobalt chloride, and cobalt naphthenate) and cobalt metal have been reported to

13   cause tumors in experimental animals, and cobalt sulfate is listed in the *Report on*

14   *Carcinogens, Eleventh Edition* as *reasonably anticipated to be a human carcinogen.*

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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 (8th or 9th 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 protions 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.

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.* 2007).

A.1.1 Potential causes of the cluster

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 military aviation base is located in Churchill County, and living near a military aviation base was hypothesized as a cause of the cluster due to the potential for population mixing (large movement of personnel occurring in the past 10 years) and potential exposure to jet fuel or benzene [although data on specific base activities or specific chemical exposures were not available]. However, Steinmaus *et al.* did not find increased risk of childhood leukemia in other U.S. counties with military aviation facilities. ATSDR (2003c) concluded that the Fallon Pipeline (which transports military jet fuel) did not pose a past public health hazard from 1970 to the present. Kinlen and Doll (2004) proposed that population mixing (the introduction of

1   infectious agents to susceptible Fallon residents by the large influx of trainees at the

2   military base) should still be explored as a suspected cause of the cluster.

3   The United States Geological Survey (USGS 2007,2008c) found in their investigation

4   that gross alpha radioactivity was higher in numerous domestic wells in Lahontan Valley,

5   which is a residential area of Fallon, in Churchill County. In 2007, the USGS sampled

6   drinking water from 1 public and 25 private wells and reported that Polonium-210

7   concentrations in some wells were five times the maximum contaminant level (MCL)

8   established by the EPA. The public water supply for Fallon and the Fallon Naval Air

9   Station was not part of the study and was considered safe. The USGS did not evaluate

10 linkages between Polonium-210 and the cancer cluster.

11 *A.1.2   Cross-sectional, case-comparison study*

12 In 2001, the Centers for Disease Control (CDC) conducted a cross-sectional, case-

13 comparison investigation that included 14 children who resided in Churchill County

14 before diagnosis of leukemia. Each case was matched on sex and age to approximately 4

15 comparison children (Rubin *et al.* 2007). Case families (parents, siblings, and adult care-

16 takers living in the house) and parents of the comparison children were also enrolled in

17 the study. A total of 14 case families and 55 comparison families were enrolled in the

18 study. Questionnaire data, biological samples, and environmental samples (indoor air,

19 play yard soil, household dust, and tap water) were collected from the study participants

20 or their homes. Biological and environmental samples were measured for heavy metals,

21 pesticides, polychlorinated biphenyls, and volatile organic compounds (VOCs). In

22 addition, biological samples were tested for viral infections, and environmental samples

23 were tested for radon and radionuclides. Questionnaire data was used to assessed

24 lifestyle and demographic factors associated with leukemia. Laboratory results were

25 compared with either levels associated with health effects or the geometric mean and 95th

26 percentile levels from the *Second National Report on Human Exposure to Environmental*

27 *Chemicals*, which is based on population data collected as part of the National Health and

28 Nutrition Examination Survey (NHANES). The results are discussed in the following

29 paragraphs.

1 *Tungsten and arsenic*

2 Environmental samples were compared with published standards for each chemical.

3 Biological sampling revealed community-wide exposure to tungsten with almost 80% of

4 the participants having urinary tungsten levels above the NHANES 90th percentile, and

5 the median tungsten levels were almost 10-fold higher than the 1999 NHANES median

6 level for tungsten. Elevated levels of tungsten were found in the tap water relative to

7 national comparison values. [Currently there is no reference level for tungsten in water.]

8 High levels of urinary tungsten also were found among residents of another Nevada

9 community (Yerington), and elevated levels were found in tap water; [urinary levels of

10 children from Churchill County were approximately 2 times higher than among children

11 in Yerington, but the levels in the total population (adults and children) were similar].

12 Urinary levels of tungsten did not differ between case and comparison children or case

13 and comparison families. Urinary levels of arsenic ranged from the limit of detection [not

14 specified] to 118.4 µg/L with a median level of 34.61 µg/L. [Arsenic levels were not

15 available in the NHANES population database.] Urinary arsenic did not differ between

16 cases and comparison children or families. Arsenic levels also were elevated in tap water

17 relative to national comparison values.

18 *Other factors*

19 Serum levels of VOCs [including benzene, which is a component of JP-8 fuel] and

20 urinary levels of pesticides were similar to national reference values. Significantly

21 elevated ORs in the case-control analyses were found for exposure to ethylbenzene (case

22 children vs. control children), and for older parental age of the father at the time of the

23 child's birth. An elevated risk for leukemia of borderline significance was found for

24 parental military service (when restricted to non-adopted children whose parent(s) were

25 in the military 1 year before the child's birth and the case child's date of diagnosis). No

26 significant associations were found between exposure to other VOCs or pesticides, or

27 other lifestyle and demographic factors (including exposure to ionizing radiation). The

28 authors concluded that the small number of cases and length of time between diagnosis

29 and exposure assessment limited their ability to find an association between leukemia and

30 environmental exposure.

1   Steinberg *et al*. (2007) conducted a study of genetic susceptibility among 11 of the 15

2   children with childhood leukemia and 42 age-and sex-matched community controls.

3   They evaluated three genes that code for enzymes that are inhibited by tungsten and may

4   affect DNA synthesis, hematopoiesis, or detoxification of contaminants. The authors

5   reported an association between the SUOX l gene locus and leukemia. Cytogenetic

6   studies did not find any evidence suggesting a common environmental exposure that

7   caused the leukemia although the authors stated the possibility could not be ruled out.

8   Analysis of pretreatment bone marrow specimens found that the chromosomal

9   aberrations and cell immunophenotypes were in the same proportions as in the general

10   population of childhood ALL cases.

11   **A.2.   Studies on exposure to cobalt and tungsten**

12   As described in Section 2 and in more detail below, a hard metal manufacturing plant is

13   located in Fallon, NV. ATSDR (2003) conducted an air exposure pathway assessment of

14   this facility. Outdoor ambient air levels were based on historical data from the Nevada

15   Bureau of Air Quality, which included data from 2 monitoring stations operating at

16   different times from 1972 to 1998, meteorological observations, and recent (2002)

17   sampling (2 locations); however, the samples were not analyzed for tungsten. They also

18   reviewed U.S. Environmental Protection Agency databases for information on air

19   emissions. ATSDR conducted air-modeling analysis of historical emissions data (pre-

20   1994 emissions) and did not find a spatial relationship between predicted exposure levels

21   for particulate matter and the location of leukemia cases. [Particulate matter emission

22   content was not reported, but was assumed to consist of several metals such as antimony,

23   arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and tungsten.]

24   No epidemiological studies were found that evaluated the relationship between exposure

25   to cobalt-tungsten hard metals and childhood leukemia.

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

27   A series of related studies by Sheppard and colleagues (Sheppard *et al*. 2006a,d;

28   Sheppard *et al*. 2007a,c,d) have reported elevated airborne tungsten and cobalt levels in

29   the vicinity of a hard-metal manufacturing facility in Fallon, Nevada. The first study

30   (Sheppard *et al*. 2006a) measured trace-metal concentrations, including tungsten and

1   cobalt, in airborne particulates collected at two different times of the year (March–April

2   and November of 2004) in Fallon and four nearby towns for comparison purposes using

3   10 portable, high-volume particulate air samplers (5 in Fallon and 5 in surrounding

4   towns) (Sheppard *et al.* 2006a,b,c). Of nineteen elements measured, only tungsten and

5   cobalt air concentrations were consistently higher in Fallon than in the surrounding

6   towns; median air levels for tungsten and cobalt were significantly ($P = 0.001$–0.002)

7   higher in Fallon than in the four comparison towns as a group.

8   Across the spring and fall sampling periods combined, median air concentrations for

9   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

10   comparison towns. For cobalt, median air concentrations ranged from 0.04 to 7.5 ng/m^3

11   in Fallon, and from 0.04 to 0.58 ng/m^3 in the comparison towns. Sheppard *et al.* (2006b)

12   noted that even when the data were presented in mass/mass units, the levels were higher.

13   Sheppard *et al.* (2006b) also noted that many other elements were measured besides

14   tungsten and cobalt, but none of them showed consistent differences or patterns between

15   Fallon and the comparison towns; and, as such they served the function of a conservative

16   trace element for the analysis. Further, Sheppard *et al.* (2006c) explained why the

17   seasonal data was analyzed individually. They noted that during their assessment, the

18   March collection period was windy, warm, dry, and but the November collection period

19   was relatively calm, cool, and wet. They noted that such a large difference in weather

20   rendered inter-seasonal comparisons of absolute values of airborne particulates of little

21   value. They noted that in both seasons, Fallon had significantly higher levels of airborne

22   tungsten and cobalt relative to comparison towns, airborne tungsten and cobalt co-varied

23   at the daily or sub-weekly scale, and wind speed correlated to at least some degree with

24   airborne tungsten levels. They concluded that replication of these patterns across two

25   different seasons provided stronger evidence for elevated tungsten and cobalt being a

26   distinctive environmental feature of Fallon than if these relative patterns had been

27   demonstrated for just one season.

28   Although tungsten is naturally present in the soils and rocks in the area (ATSDR 2003b)

29   the authors suggested that the source of cobalt and tungsten was not from a natural

30   deposit because tungsten levels were not elevated in any comparison town, tungsten and

1   cobalt particles varied temporally and spatially (indicating a single source), cobalt is not

2   naturally abundant in the area, and high winds decreased tungsten loading in Fallon. [The

3   opposite effect for tungsten loading and high winds would be expected if the source were

4   natural.] The authors investigated whether the hard-metal facility in Fallon could be the

5   source of the elevated tungsten and cobalt levels in the air. They reported that (1) loading

6   of both tungsten and cobalt dropped off steeply 3 km from the hard metal facility in

7   Fallon and then slowly beyond 3 km, and that (2) the temporal variability of tungsten and

8   cobalt loading also dropped off with distance from the hard-metal facility.

9   In a follow-up study (Sheppard *et al.* 2007b), airborne dust particles were isolated and

10   analyzed with automated electron microprobe and wavelength-dispersive spectrometry

11   revealing that the tungsten particles were generally combined with cobalt and other

12   elements such as chromium, iron, and copper, and the authors that the particles were most

13   consistent with identification as tungsten carbide. Based on the results of this analysis,

14   the authors concluded that the airborne tungsten in Fallon is anthropogenic in origin.

15   To increase the spatial resolution of tungsten and cobalt levels in Fallon, Sheppard *et al.*

16   (2007c) collected surface dust in a grid pattern within and outside of Fallon and analyzed

17   for 20 elements including tungsten and cobalt. They noted that surface dust is an ideal

18   indicator of atmospheric deposition for heavy metals and that their methodology of

19   collecting samples in a grid would allow them to map differing concentrations of

20   atmospheric deposition of heavy metals and thereby pinpoint the sources of unusual

21   airborne metals. In total, 125 surface dust samples were collected within Fallon and

22   outside of Fallon to establish background concentrations. Within Fallon, the grid cell

23   length was 0.5 km and outside of Fallon the grid cell length was extended to 2 to 5 km to

24   maximize the spatial extent of monitoring. Sampling took place after a three-week period

25   without substantial rain, and samples were taken mostly from paved surfaces. The authors

26   noted that there was little spatial variability among the measured elements except for

27   tungsten, which had a coefficient of variability of 732%. The next highest coefficient of

28   variability was cobalt at 77% followed by arsenic at 71%. The peak levels for tungsten

29   (934 ppm) and cobalt (98 ppm) overlapped exactly spatially, with the same sampling

30   location having the highest value for both. The authors reported that based on the other

1   sampling points, background levels were less than 10 ppm for tungsten and less than 15

2   ppm for cobalt. They noted that based on the results of their analysis, the source of the

3   airborne metals could be pinpointed to the vicinity of the hard-metal production facility

4   located within Fallon.

5   Sheppard *et al.* (2007d) also performed an analysis on lichens to compare airborne levels

6   of tungsten and cobalt in Fallon (N = 10) to levels at outcrops located north, east, south,

7   and west of Fallon (N = 20) and at least 20 km away from the town center. They reported

8   higher concentrations of tungsten (12.5 times higher, $P < 0.001$) and cobalt (2.0 times

9   higher, $P = 0.06$) in lichens from Fallon compared to the lichens outside of Fallon. [The

10 authors noted that lichens integrate their environment throughout their entire life and can

11 reflect atmospheric chemistry and deposition of elements across decades.] There were no

12 differences in the concentrations of tungsten or cobalt across rock samples.

13 Dendrochemistry (the study of element concentrations in tree rings) was used by

14 Sheppard *et al.* (2007a) to assess the temporal variability of tungsten and cobalt in Fallon

15 (N = 5) and three surrounding towns (N = 6). To test the accuracy of dendrochemistry for

16 tungsten, a separate analysis (validation study) using cottonwood trees and Douglas-firs

17 or cottonwood trees only was performed in a small town in Oregon with a known

18 industrial source of airborne tungsten. This study demonstrated stable levels before the

19 onset of the tungsten industry with levels increasing thereafter. The study on Fallon and

20 comparison towns used cottonwood trees. For Fallon, the authors reported that for the

21 time period from 1989 to 1992, before the onset of the leukemia cases, median tree-ring

22 tungsten levels were not statistically significantly different from the comparison towns;

23 however, thereafter, levels in Fallon increased, whereas levels in comparison towns

24 remained relatively constant. The authors noted that cobalt levels in Fallon tree rings

25 were consistently higher than in comparison towns, but there was no significant increase

26 across time within Fallon. In a separate publication, Sheppard *et al.* (2008) acknowledged

27 that during the time period that centered on 1991, there were no statistical differences

28 between Fallon and surrounding towns. However, during the time period that centered on

29 1995 [the period just before the onset of the cluster], Fallon tree-ring tungsten levels

30 started trending upward and were statistically significantly higher than levels seen in the

1   comparison towns. During the following time periods, the tungsten levels in Fallon

2   continued trending upward and remained higher than comparison towns with significance

3   levels at or near $P = 0.05$.

4   Sheppard *et al*. (2008) concluded that multiple environmental indicators have been used

5   (levels in air samples, surface dust samples, lichens, and tree rings) that incorporate

6   environmental conditions differently from one another, and yet they have all showed

7   elevated levels of tungsten in air when compared with surrounding towns. Further, they

8   concluded that tungsten particulates in Fallon are anthropogenic in origin. However, they

9   did not consider that their studies had demonstrated that exposure to tungsten caused

10 leukemia, and they pointed out the need for direct biomedical testing to establish the

11 cause of the leukemia cases.

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

13 Seiler (2006) suggested that the comparisons between towns was made based on tungsten

14 and cobalt loadings without evaluating concentrations or normalizing the loadings to a

15 conservative trace element; therefore, it was impossible to tell if the dust had higher

16 levels of tungsten and cobalt, or if Fallon was simply a dustier town. Sueker (2006) also

17 commented that the data, as presented in Sheppard *et al*. (2006a) did not allow for the

18 determination of whether tungsten and cobalt were more abundant in the dust or if Fallon

19 were simply dustier. Seiler noted that the data presented by Sheppard did not confirm the

20 presence of tungsten carbide but only of tungsten in the particulate matter. Seiler also

21 suggested that Sheppard *et al*. did not account for the possibility of higher tungsten levels

22 in the dust simply due to its unique geohydrologic history.

23 Sueker (2006) expressed concerns about the way wind speed and direction was used in

24 the Sheppard assessment. Sueker noted that Sheppard *et al*. developed two regressions for

25 the two seasonal sampling periods, and that if these data were pooled, the relationship

26 between wind speed and loadings disappeared. Similarly, Sueker noted that if outliers

27 that Sheppard omitted from the analysis [without satisfactory explanation] were included,

28 the relationship disappeared.

1   Sueker (2006) made note of the report by Sheppard that tungsten loadings dropped off

2   rapidly to typical ambient loadings within 2 km of the hard-metal facility. She pointed

3   out, however, that many of the homes of the leukemia cases fall outside of the modeled

4   impacted area and cited the ATSDR 2003 study on air exposure pathway assessment of

5   this facility discussed above.

6   Schell and Pardus (2007) commented on the Sheppard *et al*. dendrochemistry study and

7   suggested that the data do not support the conclusions drawn; but rather, if the data

8   support anything, it is that the cobalt and tungsten levels are not causally related. Based

9   on an evaluation of graphic representations of the data presented in Sheppard *et al*.

10   (2007a) (they noted that the data were not provided) the authors suggested that the

11   increase in tungsten levels in the trees actually occurred during the 2001 to 2004 time

12   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 (U.S., NR)
scrap loader	192 {1}		9	
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, "S = stationary sampling	Kraus *et al*. 2001 (Germany, NR)
Production of WC	P: 0.39 {1}	2.1 (0.31–5.7)[b] {4}	Only the range was presented for air monitoring data, single values reflect samples of N = 1	
Powder processing	P: NR (7.9–64.3) {4}	28.5 (0.75–227.8)[b] {14}		
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}		

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)
Forming " Pressing Sintering " Heavy alloy prod. Maintenance	P: NR (7.8–97.4) {5} S: 6.2 {1} P: NR (5.3–211.0) {3} P: 12.1 {1} S: 5.9 {1} P: NR (125.0–417.0) {2} S: NR (50.0–163.0) {3} NA	10.7 (0.33–33.1)[b] {23} NA 8.6 (1.5–71.0)[b] {30} 12.5 (2.1–46.8)[b] {6} NA 24.9 (2.6–50.5)[b] {3} NA 3.4 (1.5–5.3)[b] {2}		
Powder preparation rotation full-time Press rubber steel Shaping Sintering	459 (7–6,390) {60} 147 (26–378) {12} 339 (48–2,910) {26} 47 (6–248) {34} 97 (4–1,160) {179} 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 (2) Sintering	(1) 141 (9–436) {9} (2) 25 (7–51) {18}	*Urine* (1) 1 {1} (2) 2 {1} *Blood (µg/dL)* (1) 0.42 {1} (2) 0.28 {1} *Hair (ppm)* (1) 25.8 {1} (2) NA	Data are for two employees from a study of 4 subjects with occupational asthma Exposure levels for subjects 3 and 4, who performed grinding tasks, are presented in Table B-2	Kusaka 1996 (Japan, NR)
Weighing (across 3 factories)	*Cobalt* S: 106–478 (NR) {NR}	CoB 45.6 (1–245) {88} CoU 303.6 (0.75–5,500) {88}	"S" = stationary sampling, "P" = personal sampling < 7 µm is the concentration in the air	Sabbioni *et al.* 1994a (Bergamo Province, Italy, 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)
	P: 418–1,600 (NR) {NR} < 7 µm: 12–27 {NR} *Tungsten* S: 0.14–32 (NR) {NR} P: 0.73–150 (NR) {NR} < 7 µm: 0.023–3.1 (NR) {NR}	CoH 49.1 (110–910,000)[c] {90} CoN 53.792 (109–580,000)[c] {92} WB 1.2 (0.04–6.5) {43} WU 6.7 (0.11–230) {78} WH 2,147 (25–59,000)[c] {75} WN 3,056 (27–105,000)[c] {82}	fraction measuring than 7 microns (considered respirable) measured by stationary sampling Biological data were aggregated and summarized across workers irrespective of production stage or factory Exposure levels for workers involved in grinding operations presented in Table B-2	Italy, NR)
Mixing of hard-metal powders for production of diamond wheels	**Workers assessed for Co** 240 (19–1,360) {70} **Subset of workers assessed for Co and W** *cobalt* 170 (20–350) {23} *tungsten* 26 (3–210) {23}	*Beginning of workweek* 42.6 (10.7–100.2) {70} *End of workweek* 71.3 (16.1–210.4) {70} **Subset of workers** *cobalt* 61.1 (13–262) {23} *tungsten* 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 ($r = 0.78$, $P < 0.001$). The number of samples not explicitly stated, but inferred from text.	Sabbioni *et al.* 1994a (Pavia, Italy, NR)
Before ventilation Mixing Forming Pressing *After ventilation* Mixing Forming Pressing	245[d] (96–967) {6} 772[d] (181–5,270) {10} 82[d] (40–541) {7} 50[d] (12–127) {9} 82[d] (15–190) {18} 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)
Diamond abrasive production			A total of 250 air samples and greater than 600 biological samples taken for	Mosconi *et al.* 1994 (Italy, 1991)

Stage of the hard-metal production process	Air Concentration Mean (Range) {N} $\mu g/m^3$	Biological levels[a] Mean (range) [N] $\mu g/L$	Additional information	Reference (Location, year of measurement)
production mold filling	S: 220[e] (47–960) {NR} P: 382[e] (76–2,600) {NR}	587 (39–2,100) {NR}	this study (data for grinders presented in Table B-2); however, number of samples not provided for specific subgroups	(Italy, 1991)
sintering	S: 102[e] (32–240) {NR} P: 309[e] (238–413) {NR}	193 (102–390) {NR}		
mechanical working	S: 20[e] (12–44) {NR} P: 40[e] (7.1–65) {NR}	67.2 (14–165) {NR}		
Tool production	S: 6[e] (5–47) {NR} P: 17[e] (4–28) {NR}	19.4 (0.8–100) {NR}		
Hard metal alloy filling	S: 2[e] (0.8–3) {NR} P: 5[e] (1–107) {NR}	4.8 (0.8–18) {NR}		
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 Press rubber machine Shaping Sintering	688 (6–6,388) {38} 473 (48–2,905) {19} 85 (4–407) {27} 126 (6–1,155) {129} 28 (2–145) {38}	NA	Exposure data for workers engaged in blasting, electron discharging, and wet and dry grinding are provided in Table B-2	Kusaka *et al.* 1986b (Japan, 1981–1984)
Sawing Pressing/mixing Sintering Supervision Remainder Office	4.3 (0.3–15) mg/m³ dust {NR} Cobalt content ranged from 4% to 17%: authors noted a daily load of about 3 mg cobalt per day.	*Urinary cobalt levels* 64.3 (45–102) {3} 45.1 (31–56) {4} 6.4 (2.5–11.1) {3} 11.7 (5.5–25) {5} 11.3 (8.1–14.4) {2} 4.6 (0.3–13.6) {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 $\mu g/g$ creatinine and noted that clear evidence of cobalt	Posma and Dijstelberger *et al.* 1985 (The Netherlands, 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)
Sawing Pressing/mixing Sintering Supervision Remainder Office		*Serum cobalt levels* 18.3 (9.6–32) {3} 11.5 (10.4–12.9) {4} 2.0 (< 0.3–4.4) {3} 2.5 (1.4–4.4) {5} 3.5 (2.2–4.8) {2} <0.3 (<0.3) {5}	exposure. Exposure data from grinding operations are presented in Table B-2	
Powder handlers Rubber press operators Automatic press operators Shapers (lathing) Shapers (sawing) Sintering workers Workers using respirators Office workers	186 (110–262) {2} 367 (92–859) {6} 56 (9–210) {11} 33 (15–62) {7} 50 (8–144) {21} 28 (4–145) {21} 317 (7–1,203) {25} NA	*Urinary cobalt levels* 148 (138–158) {2} 235 (41–392) {6} 34 (4–73) {11} 33 (11–95) {7} 41 (6–266) {21} 10 (2–46) {21} 26 (1–119) {25} 2 (1–4) {20}	*Blood cobalt levels (μg/dL)* 1.08 (0.88–1.28) {2} 1.87 (0.4–5.3) {6} 0.57 (0.1–0.95) {11} 0.67 (0.14–1.34) {7} 0.52 (0.15–1.15) {21} 0.26 (0.09–0.45) {21} 0.65 (0.2–3.9) {25} 0.19 (0.08–0.4) {20}	Ichikawa *et al.* 1985 (Japan, NR)
Hand pressing Automatic pressing Forming Sintering Finishing (testing) Maintenance	maximum > 100 {NR} maximum > 10 {NR} maximum > 50 {NR} maximum < 10 {NR} maximum > 10 {NR} maximum > 50 {NR}	Monday: up to 36 {26} Friday: 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 Weighing & mixing Milling	32,470 (44–438,000) {18} 8,661 (91–48,148) {13}	NA	Sampling was conducted in a manner to obtain peak exposure levels. Authors noted that they found peak air concentrations of cobalt exceeding 500	Sprince *et al.* 1984 (United States, 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)
Drying	235 (100–375) {4}		µg/m³ during many major steps in the production of cemented carbides. Data for grinding operations provided in Table B-2	
Pressing	755 (13–7,359) {14}			
Machining	94 (2–336) {21}			
Reclaiming	671 (189–1,708) {7}			
Plant B				
Weighing & mixing	327 (20–1,480) {17}			
Milling	282 (15–800) {6}			
Drying	337 (36–640) {6}			
Pressing	326 (40–769) {9}			
Machining	116 (7–504) {12}			
Reclaiming	214 (114–342) {11}			
Producing cobalt powder	NR (675–10,000) {NR}	35.1 (NR) {NR}	No additional information provided	Pellet *et al.* 1984 as cited in Angerer and Heinrich 1988 (NR, NR)
Producing presintered tungsten carbide	NR (120–284) {NR}	9.6 (NR) {NR}		
Using hard metal	NR (180–193) {NR}	11.7 (NR) {NR}		
Powder mixing	48 (NR) {NR}	NA	Cobalt air concentration in worker's breathing zone. Maximum value detected was 170 µg/m³.	NIOSH 1981 (United States, 1977–1978)
Pressing	33 (NR) {NR}			
General maintenance	25 (NR) {NR}			
Cobalt		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). 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 (United States, Austria, Switzerland, Sweden, former USSR, NR)
Powder processing	0–2,720 {NR}			
Tool & die operations	10–230 {NR}			
Casting	0–6,800 {NR}			
Forming	10–1,750 {NR}			
Tungsten				
Powder processing	880–25,600 {NR}			
Tool & die operations	NA			

Stage of the hard-metal production process	Air Concentration Mean (Range) {N} $\mu g/m^3$	Biological levels[a] Mean (range) [N] $\mu g/L$	Additional information	Reference (Location, year of measurement)
Casting	520–17,600 {NR}			
Forming	80–26,700{NR}			
General air samples			Lowest detected level for metal preparation was 10 $\mu g/m^3$	McDermott *et al.* 1971
metal preparation	(NR) 0–140 {14}			(U.S., NR)
forming	(NR) 10–150 {16}			
sintering	(NR) 5–140 {8}		Detail on differences between the two types of presses not provided; lowest detected level for blank presses was 10 $\mu g/m^3$	
Press operations				
slug presses	(NR) 10–900 {8}			
blank presses	(NR) 0–400 {18}			
Machine tool operations			Machine tool operations are pre-sintering steps. The lowest detected level for surface grinding was 1 $\mu g/m^3$ (see Table B-2 for exposure levels from post-sintering grinding operations) and the lowest detected level for drilling was 20 $\mu g/m^3$. The second highest level for slicers was 800 $\mu g/m^3$ and the second highest level for pelletizers was 250 $\mu g/m^3$.	
lathes	(NR) 10–800 {12}			
surface grinders	(NR) 0.0–800 {32}			
milling	(NR) 10 (for all samples) {3}			
drilling	(NR) 0–100 {6}			
saws	(NR) 10–400 {10}			
slicers	(NR) 10–4,600 {7}			
pelletizers	(NR) 30–2,160 {6}			
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}			

N = number of samples, NR = not reported, NA = not assessed, CoA = cobalt in air, CoB = cobalt in blood, CoN = cobalt in toenails, CoH = cobalt in hair, WA = tungsten in air, WB = tungsten in blood, WN = tungsten in toenails, WH = tungsten in hair.
[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} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
Dry grinding Area located near dry-grinding operations	Dust: 128 $\mu g/m^3$ {1} Coalt: 1 $\mu g/m^3$ {1} Dust: 229 $\mu g/m^3$ {1} Coalt: 1 $\mu g/m^3$ {1}	NA	Respiratory mass fraction was reported to be 37% for dry grinder 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 (United States, NR)
(A) Powder mixing or dry-grinding (B) Powder mixing or dry-grinding (C) Grinding	Cobalt[b] (A) 8.25[c] (0.1–16.4) {NR} (B) 8.45[c] (0.9–16.0) {NR} (C) 26.0[c] (14.6–37.4) {NR} Tungsten[b] (A) < 0.01[c] {NR} (B) 0.1[c] (0.01–0.2) {NR} (C) 3.0[c] (1.1–4.9) {NR}	Cobalt[d] (A) [1.5[c] (0.9–2.8)[e]] {10} (B) [26[c] (8.4–190)[e]] {11} (C) [9.8[c] (3.7–25.6)[e]] {12} (D) [0.05[c] (0.03–0.2)[e]] {16} Tungsten[d] (A) [< 0.1[c] (< 0.1–1.6)[e]] {10} (B) [2.0[c] (1.0–8.0)[e]] {11} (C) [13.4[c] (5.2–26.4[e])] {12} (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. For urine analysis, group D was a control group consisting of non-exposed workers. Urinary levels presented for end-of-shift, and in units of $\mu mol/mol$ creatinine in source paper with conversion units provided by authors.	Goldoni *et al.* 2004 (Italy, NR)
Wet and dry grinding operations	*Cobalt* Wet: 0.2 {1} Dry: 0.48 {1} *Tungsten* Wet: 3.3 {1} Dry: 81.3 {1}	*Cobalt* 2.2 (0.19–6.0) {5} *Tungsten* 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 (Germany, NR)

Operation	Air concentration Mean (Range) {N} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
Hard-metal and stellite saw-blade grinding, brazing, and welding	*Before ventilation installed* 51–146 (10–346) {12} *After ventilation installed* 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 products. Presented are the range of means and full range across the 4 workers	Simcox *et al.* 2000 (United States, 1995)
Grinding hard-metal and stellite blades	NR ([1–70]) {91}	14.2 (0.5–160) {131}	Measurements from 16 workplaces. Air range estimated from graph.	Linnainmaa and Kiilunen 1997 (Finland, NR)
Tool manufacturing and blade repair	Dust: 1,200[f] (300–10,400) {87} Cobalt: 17[f] (2–240) {87}	NA	These results include data for grinding of stellite. 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 (Finland, NR)
Blasting Electron discharging Grinding	2 (1–4) {7} 3 (1–12) {18} 45 (1–482) {517}	NA	See Table B-1 for production exposure levels from this study.	Kumagai *et al.* 1996 (Japan, NR)
Grinding	(3) 31 (21–40) {3} (4) 6 (2–12) {10}	*Urine* (3) 29 {1} (4) 9 {1} *Blood* (3) 0.40 ($\mu g/dL$) {1} (4) 0.32 ($\mu g/dL$) {1} *Hair* (3) 9.11 (ppm) {1} (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 (Japan, NR)
Grinding hard-metal	*Before*	*Before*[g]	"Before" and "After" refer to before and after	Linnainmaa 1995

Operation	Air concentration Mean (Range) {N} (µg/m³)	Biological Levels[a] Mean (Range) {N} (µg/L)	Additional information	Reference (location, year of measurement)
blades	(A) NR (9–39) {15} (B) NR (16–160) {8} (C) NR (6–33) {21} (D) NA (E) NR (3–91) {25} (F) NR (1–7) {18} *After* (A) NR (< 2) {12} (B) NR (< 3) {6} (C) NR (3–15) {6} (D) NR (< 1) {3} (E) NR (12–27) {7} (F) NR (2–28) {9}	(A) NR (9.2–17) {5} (B) NR (8.4–19) {3} (C) NR (26–44) {6} (D) NA (E) NR (6.1–63) {10} (F) NR (13–15) {2} *After*[g] (A) NR (0.4–3.1) {9} (B) NR (0.5–0.6) {2} (C) 13 {1} (D) 1.8 {1} (E) NR (11–62) {5} (F) NR (18–27) {2}	engineering controls installed. Designations of A through F refer to different facilities that were assessed.	(Finland, NR)
Grinding of hard-metal and stellite 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/m³. 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) Grinding hard metal tools (23 factories)	S: 22[c] (15–45) {NR} P: 230[c] (82–690) {NR} S: 5[c] (2.5–94) {NR} P: 9.3[c] (1.5–178) {NR}	151 (34–520) {NR} 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)
Wet and dry	0.0036–0.350 (NR) {23}	0–40.25 (0–86) {48}	Analysis of 12 manufacturing facilities. For	Imbrogno and

Operation	Air concentration Mean (Range) {N} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
grinding and sharpening			air levels, mean data presented for 10 facilities. For urinary data, range of mean data and full range across all 12 facilities presented.	Alborghetti 1994 (Italy, NR)
Wet grinding hard-metal tools (3 factories)	**Factory A** *Before* Mon.: 376[f] ± 2.2[h] {10} Fri.: 91[f] ± 2.4[h] {10} *After* Mon.: NA Fri.: 9.9[f] ± 1.5[h] {10} **Factory B** Mon.: 8.7[f] ± 3.9[h] {10} Fri.: 19.1[f] ± 2.8[h] {10} **Factory C** Mon.: 13.1[f] ± 1.8[h] {6} Fri.: 6.4[f] ± 3.5[h] {4}	**Factory A** *Before* Mon.: 138.3 ± 108[i] {3} Fri.: 123.7 ± 74[i] {3} *After* Mon.: NA Fri.: NA **Factory B** Mon.: 15.3 ± 7.7[i] {5} Fri.: 24.4 ± 14.1[i] {5} **Factory C** Mon.: 48.2 ± 7.3[i] {3} Fri.: 74.7 ± 13[i] {3}	Factories A, B, and C refer to three different facilities that performed wet-grinding of hard-metal tools. "Before" and "After" are in reference to measurements taken before and after installation of a ventilation system. "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* P: 91[f] (5.0–1,338) {51} S: 40[f] (5.0–110) {52} *With* P: 9[f] (1.0–38) {55} S: 12[f] (4.0–58) {47}	NA	"With" and "Without" refer to facilities with and without ventilation systems. "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[f] (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)
Grinding/sharpening	NA	17 nmol/mmol CR {~150}		White and Dyne

Operation	Air concentration Mean (Range) {N} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
of hard-metal tools				1994 (United Kingdom, NR)
16 small "Widia" (hard metal) tool grinding facilities	*Without* F: 6.68[f] ± 2.27[h] {16} P: 47.75[f] ± 3.53[h] {18} *With* F: 3.47[f] ± 2.15[h] {6} P: 4.43[f] ± 2.7[h] {17}	28.5[f] ± 3.97[h] {6} 2.66[f] ± 1.69[h] {8}	"With" and "without" refer to the use of machines with aspirators. "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* S: 64–245 (NR) {NR} P: 288–985 (NR) {NR} < 7 μm: 4–14 (NR) {NR} *Tungsten* S: 2.1–62 (NR) {NR} P: 22–77 (NR) {NR} < 7 μm: 0.13–2.4 (NR) {NR}	CoB 45.6 (1–245) {88} CoU 303.6 (0.75–5,500) {88} CoH 49.1 (110–910,000)[j] {90} CoN 53.792 (109–580,000)[j] {92} WB 1.2 (0.04–6.5) {43} WU 6.7 (0.11–230) {78} WH 2,147 (25–59,000)[j] {75} WN 3,056 (27–105,000)[j] {82}	"S" = stationary sampling, "P" = personal sampling. < 7 μm is the concentration in the air fraction measuring than 7 microns (considered respirable) measured by stationary sampling. Biological data were aggregated and summarized across all workers irrespective of production stage or factory. Exposure levels for workers involved in weighing operations presented in Table B-1	Sabbioni *et al.* 1994a (Bergamo Province, Italy, NR)
Grinding operations in the production of carbide-tip saw blades	**(A)** *Total Co* 14–73 (NR) {24} *Respirable Co* 11 (2–28) {24} **(B)** 54 & 58 (NR) {8} **(C)** [87.4] (0.05–0.194) {5}	*Overall* NR (2.6–38) {13} *Wet grinding operations* 33.6 ± 6.5[i] {2} *Dry grinding operations* 12.2 ± 6.2[i] {4}	Group A 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. Group B provides the means of two sets of 4 personal samples. Group C data are results for 5 single, personal air samples.	Stebbins *et al.* 1992 (United States, NR)

Operation	Air concentration Mean (Range) {N} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
			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 (Japan, NR)
Four workers involved in sharpening and grinding operations	NA	*Urine* (1) [5.0] (2.5–8) {3} (2) 20 {1} (3) 35 {1} (4) 15 {1} *Blood* (1) [4.27] (1.5–9) {3} (2) 4 {1} (3) 4.9 {1} (4) 2.5 {1} ***Tungsten*** *Urine* (1) [347] (2–1,000) {3} (2) 60 {1} (3) 30 {1} (4) 20 {1} *Blood* (1) [20.73] (0.9–60) {3} (2) 0.7 {1} (3) 1.0 {1} (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. 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 (Italy, NR)
Grinding, sharpening, and	*Respirable*	NR (ND–7.6) {63}	Air levels include both personal and stationary monitoring results.	Burr and Singal (United States,

Operation	Air concentration Mean (Range) {N} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
tooling of hard-metals	4 (ND–4) {31} *Total* 30.2 (ND–97) {33}		Means for air levels were calculated from only the data above the detection limit (only 1 sample above detection for respirable cobalt). Only thirty percent of urine samples exceeded the detection limit of 3.4 $\mu g/L$.	NR)
Saw blade and tool sharpening	*Cobalt* (A) [45] (26–63) {2} (B) [9.38] (2.8–14) {4} (C) 30 {1} *Tungsten* (A) [645] (365–925) {2} (B) [186] (ND–261) {4} (C) NA	*Cobalt* *Pre-shift urine sample* (A) [13.5] (ND–19.1)[d] {8} (D) [7.2] (4.9–9.5)[d] {4} (E) [2.74] (1.8–4.1)[d] {12} *Post-shift urine sample* (A) [18.3] (12.9–23.8)[d] {8} (D) [7.6] (7.2–8.0)[d] {4} (E) [6.0] (2.6–13.2)[d] {12} *Tungsten* 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. Group B consisted of 4 area samples. For tungsten, the mean was calculated from the 3 values that were above the limit of quantitation. Group C was a single measurement for cobalt from the outlet of an exhaust system that filtered and recirculated air in the workshop. Group D was one truck driver who spent several hours per day in the workshop. Group E was a control group of office workers.	Tharr and Singal 1987 (United States, NR)
Finish grinding of hard-metal cutting tool inserts	*Respirable Cobalt* [4.3] (ND–8.4) {24} *Total Cobalt* 13.5 (ND–26.8) {24} *Tungsten* 280 (ND–410) {24}	*Pre-shift* 10.5 (4.7–19)[d] {10} *Post-shift* 18.09 (8.4–27.7)[d] {10}	Mean air levels were calculated from only the values above the detection limit. 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	Bryant and Singal 1987 (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)
			(P = 0.003). [Tungsten in air assumed total.]	
Blasting Electron discharging Grinding wet dry	3 (1–4) {5} 4 (1–5) {5} 53 (11–1,247) {205} 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. 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} (B) 45 (3–161) {18} (C) 92 (15–291) {12} (D) 44 (3–205) {25} (E) 317 (7–1,203) {25} (F) NA	*Urine* (A) 35 (2–180) {27} (B) 19 (2–67) {18} (C) 68 (3–265) {12} (D) 17 (1–69) {25} (E) 26 (1–119) {25} (F) 2 (1–4) {20} *Blood* (A) 4.2 (1.0–13) {27} (B) 3.3 (1.6–5.2) {18} (C) 4.3 (1.2–19) {12} (D) 3.5 (1.0–10) {25} (E) 6.5 (2–39) {25} (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. "E" is a group of workers who used respirators. "F" was a group of office workers used as unexposed controls. Exposure levels for workers performing other tasks presented in Table B-1	Ichikawa *et al.* 1985 (Japan, NR)
Grinding operations in a hard-metal factory	*Dust* 4.3 (0.3–15) mg/m^3 {NR} *Cobalt* 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	Posma and Dijstelberger 1985 (The Netherlands, NR)

Operation	Air concentration Mean (Range) {N} ($\mu g/m^3$)	Biological Levels[a] Mean (Range) {N} ($\mu g/L$)	Additional information	Reference (location, year of measurement)
day)			clear evidence of cobalt exposure. Exposure data from other operations are presented in Table B-1	
Grinding operations at 2 hard-metal production facilities	118 (12–307) {5} 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* 2,100 (1,500–3,000) {4} *Cobalt* 7–9% of dust concentration *Tungsten* 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 (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 (NR, 1977–1978)
Dry grinding without exhaust	NR (40–2,440) {NR}	NA	No additional information provided	NIOSH 1977 (Switzerland, NR)
Wet grinding of hard-metal tools	*Cobalt* S: 280 (40–930) {25} P: 240 (30–560) {12} *Tungsten* S: 5,160 (< 200–12,800) {25} P: 3,930 (720–8,060) {12}	NA	"S" is for stationary sampling and "P" is for personal sampling results A small follow-up study after ventilation controls installed showed cobalt levels below detection limits	Lichtenstein 1975 (United States, NR)

N = number of samples, CR = creatinine, ND = not detected, NR = not reported; NA = not assessed; ND = below the limit of quantitation, CoA = cobalt in air, CoB = cobalt in blood, CoN = cobalt in toenails, CoH = cobalt in hair, WA = tungsten in air, WB = tungsten in blood, WN = tungsten in toenails, WH = tungsten in hair.
[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] Geometric mean.
[g] 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.
[h] Geometric standard deviation.
[i] Standard deviation.
[j] ng/g