

Cobalt-Tungsten Carbide Powders and Hard Metals Expert Panel Report

Part B – Recommendation for Listing Status for Cobalt-Tungsten Carbide Powders and Hard Metals and Scientific Justification for the Recommendation

The Report on Carcinogens (RoC) expert panel for cobalt-tungsten carbide powders and hard metals exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, North Carolina on December 9-10, 2008, to peer review the draft background document on cobalt-tungsten carbide powders and hard metals exposures and make a recommendation for their listing status in the 12th Edition of the RoC.

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The expert panel's recommendation for listing status and the scientific justification for their recommendation follow.

Overall Evaluation

Following a discussion of the body of knowledge, the expert panel reviewed the RoC listing criteria and unanimously recommended by a vote of 6 yes/0 no that cobalt-tungsten carbide powders and hard metals should be listed in the RoC as *reasonably anticipated to be a human carcinogen*, based on limited evidence in humans and supporting mechanistic data.

The major considerations that led the panel to its recommendation are discussed below.

We identified occupational epidemiological studies of workers exposed to powders and hard metals of cobalt-tungsten carbide, with evidence of a statistically significant excess of lung

cancer with a positive dose-response relationship. Chance, bias, and confounding are unlikely to explain the observed lung cancer excess. Cobalt-tungsten carbide releases substantial amounts of cobalt ions in both *in vivo* and *in vitro* studies. Clear evidence of carcinogenicity of soluble cobalt compounds from animal studies and compelling animal and *in vitro* data of genotoxicity were major factors in our assessment, in addition to epidemiologic studies in workers. Cobalt ions act at a number of molecular cancer-related targets based upon both *in vivo* and *in vitro* studies, to potentially induce tumors. Cobalt ions act at a number of molecular cancer-related targets based upon both *in vivo* and *in vitro* studies, to potentially induce tumors; the targets include (1) DNA damage, (2) generation of reactive oxygen species which can also produce oxidative DNA damage and activate cell signaling pathways, (3) inhibition of the activity of the dioxygenase superfamily of enzymes that activate hypoxia signaling, cause epigenetic effects and inhibit oxidative repair of DNA damage, (4) inhibition of repair of endogenous and environmentally induced DNA damage, and (5) activity as a tumor promoter and co-carcinogen. Based upon these data, collectively, powders and hard metals of cobalt-tungsten carbide were determined to be *reasonably anticipated to be a human carcinogen*.

Our conclusions are in agreement with previous evaluations. To date, international IARC, German and American occupational/environmental health agencies have concluded that:

- Tungsten-carbide/cobalt is *probably carcinogenic* (IARC, 2006 category 2A) or *carcinogenic* (German MAK 2007, category 1),
- Cobalt metal and its compounds are *possibly carcinogenic* (IARC, 2006 category 2B) or should be *considered as carcinogenic* based on experimental results (MAK 2007, category 1).
- Cobalt sulfate has been proclaimed as “*reasonably anticipated to be a human carcinogen*” by NTP (2002).

It was suggested by the panel that the title of the nomination be changed to “Powders and Hard Metals of Cobalt-Tungsten Carbide.”

The panel voted 6 yes/0 no to accept the scientific justification for powders and hard metals of cobalt-tungsten carbide to be listed as *reasonably anticipated to be a human carcinogen*.

Human Exposure

There are numerous studies across a variety of industries and job categories to demonstrate worker exposures in the United States to cobalt-tungsten carbide powders and hard metals. Worker exposures are documented in manufacturing processes (including both unsintered and sintered materials), reclamation and recovery operations, and reconditioning and repair of hard metal tools. Limited data were found documenting cobalt and tungsten exposures from hard metal use. Criteria from OSHA, NIOSH, and ACGIH may be used as guidelines for evaluating cobalt and tungsten exposure concentrations found in the literature. Studies clearly show workers have been exposed to concentrations exceeding current exposure criteria. Numerous studies involving air and biological monitoring have shown that cobalt exposures vary depending on time of sampling, type of processing, job, and degree of engineering controls. Cobalt levels have most commonly been used as the indicator of exposure to cobalt-tungsten carbide hard metals. Biomonitoring data of cobalt in urine, blood, and in a few cases other biological samples such as hair and nails have been collected. Biological monitoring of workers confirmed absorption of cobalt and tungsten into the body.

Exposure assessment studies used both personal and stationary air sampling methods to document worker exposure. Different sampling methods, flow rates, and sampling times were used across the studies. Although varying sampling methods were used, the data clearly

demonstrate worker exposure to cobalt and tungsten, and allow for characterization of the differences in exposures across industry and jobs. Potential confounders that exist in the tungsten carbide industry include asbestos, polyaromatic hydrocarbons, crystalline silica, and other metals such as nickel and chromium.

Human Cancer Studies

1. *Principal studies*

Moulin *et al.* (1998), Hogstedt and Alexandersson (1990), Wild *et al.* (2000). Moulin *et al.* and Hogstedt and Alexandersson reported results from multi-plant studies in France and Sweden, respectively. Wild *et al.* provided more detailed analyses for a subgroup of the French cohort.

2. *Findings*

2.1 *Overall findings*

Both multi-plant studies (Moulin *et al.* and Hogstedt and Alexandersson) found excess lung cancer relative to the general population in a cohort analysis; the standard mortality ratio (SMR) was about 1.3. The SMR was statistically significant in the French study (Moulin *et al.*), which had over two times the number of workers and deaths as the Swedish study (Hogstedt and Alexandersson). In the nested case-control analysis of the French cohort, the overall odds ratio (OR) for lung cancer in the exposed (exposure levels 2-9) versus little or un-exposed (exposure levels 0-1) was 1.93 (95% confidence interval [CI] = 1.03 to 3.62). Internal analyses are usually assumed to be less affected by confounding than SMRs, and the results are not diluted by inclusion of unexposed workers, so the OR from the French study may be a better estimate of the excess risk associated with exposure to tungsten carbide and cobalt.

- Moulin *et al.* reported statistically significant, increasing trends in ORs for duration of exposure at levels ≥ 2 and unweighted cumulative dose. ORs for workers at the highest level of estimated exposure ranged from 2.03 to 4.13; these were statistically significant for 2 of the 4 exposure metrics and of borderline significance for a third metric.
- Hogstedt and Alexandersson did not report consistent patterns of response with increases in the duration or estimated level of exposure in the Swedish cohort, although the study was limited by small sample size in subgroups defined by exposure and latency. The SMRs for workers in the low- and high-exposure groups were 2.27 and 3.33, respectively, based on 3 to 4 deaths in each category in the group with the highest estimated exposure and longest latency. All workers with ≥ 10 years exposure and > 20 years latency had an SMR of 2.78 (95% CI = 1.11 to 5.72).

2.2 *Exposure-response relationship*

There was evidence of an exposure-response relationship for lung cancer in these studies

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- Hogstedt and Alexandersson did not report consistent patterns of response with increases in the duration or estimated level of exposure in the Swedish cohort, although the study was limited by small sample size in subgroups defined by exposure and latency. The SMRs for workers in the low- and high-exposure groups were 2.27 and 3.33, respectively, based on 3 to 4 deaths in each category in the group with the

highest estimated exposure and longest latency. All workers with more ≥ 10 years exposure and > 20 years latency had an SMR of 2.78 (95% CI = 1.11 to 5.72).

2.3 Latency

Latency was not examined in the French cohort. In the Swedish cohort workers with ≥ 10 years exposure and > 20 years latency had an SMR of 2.78 (95% CI = 1.11 to 5.72), as noted above.

2.4 Effect of Sintering

Moulin *et al.* identified higher risk associated with exposure prior to sintering (OR = 1.69, 95% CI = 0.88 to 3.27) compared with after sintering (OR = 1.26, 95% CI = 0.66 to 2.40). ORs for before-sintering exposures increased significantly with increasing frequency-weighted cumulative exposure, suggesting an exposure-response effect. In more detailed analyses of the largest plant included in the French study, Wild *et al.* reported a statistically significant relative risk (RR) of 1.43 per 10 years of exposure to unsintered cobalt-tungsten carbide and a non-significant RR of 0.75 for presence versus absence of exposure to sintered cobalt-tungsten carbide alone.

Wild *et al.* also reported SMRs of 2.86 among workers exposed only to unsintered material and 1.14 among workers exposed only after sintering; sample size in these comparisons was small, however, and confidence intervals were wide. These findings are suggestive of higher risk among workers exposed only to unsintered materials, but the data are insufficient to support firm conclusions. Furthermore, it is not possible to determine whether the apparent difference in risk before or after sintering is a result of differences in the level of exposure or in the chemical or physical properties of the materials.

3. Limitations

3.1 Confounding

As in many occupational studies there was limited ability to control for confounding in this literature. However, the potential for confounding related to smoking and exposure to workplace lung carcinogens was addressed in the Moulin *et al.* study, which included measurements of ever vs. never smoking through interviews primarily with colleagues and relatives and assessment of exposure to other workplace carcinogens through the job-exposure matrix (JEM).

3.1.1 Smoking

- There was no evidence of confounding by smoking in the French cohort. Moulin *et al.* reported a crude OR of 2.29 versus a smoking-adjusted OR of 2.60 with overlapping CIs.
- For the Swedish study, Hogstedt and Alexandersson reported that the proportion of current and former smokers in the Swedish cohort was similar to that of the national general population.
- Mortality from other smoking-related diseases also suggests limited potential for confounding. In the French cohort, mortality from chronic bronchitis and emphysema was notably depressed (SMR = 0.40, 95% CI = 0.05 to 1.44) and there was no consistent pattern of mortality for other smoking-related cancers, including cancers of the larynx, bladder, buccal cavity/pharynx and esophagus. The Swedish cohort showed an SMR of 1.31 (95% CI = 0.52 to 2.70) among all workers for chronic obstructive pulmonary diseases, a category that includes emphysema.

3.1.2 Other Occupational Carcinogens

- Moulin and Wild considered 9 IARC-designated carcinogens for which exposure was coded as present or absent in the JEM for the French cohort. Moulin reported that

adjustment for exposure to other carcinogens did not change the OR for simultaneous exposure to cobalt and tungsten-carbide.

- In further analyses of workers in one of the French plants, Wild reported a RR of 1.48 for exposure to any IARC carcinogen without considering exposure to cobalt-tungsten carbide. SMRs for exposure to unsintered cobalt-tungsten carbide were similarly elevated among workers with and without exposure to IARC carcinogens. Wild also reported SMRs for workers exposed only to sintered cobalt-tungsten carbide, but precision was too limited to reach conclusions about the effect of IARC carcinogens in this group.
- No information was given on exposure to other workplace carcinogens in the Swedish cohort.

3.2 Exposure Measurement Error

Exposures for both the French and Swedish cohorts were assessed semi-quantitatively. Two exposure groups were considered in analyses of the Swedish study. The French study used expert judgment and limited available data to construct a JEM. Semi-quantitative assessments are commonly used, although they are less informative than quantitative ones and do not allow estimation of the risk per unit of exposure. Semi-quantitative exposure scores in the French study were significantly correlated with the available measurements of cobalt in air, but exposures were not uniform within groups and sample sizes within exposure groups were small, reducing the precision of the estimate.

In most cases such random errors in estimating exposure lead to attenuation of observed exposure-response relationships toward the null value. Exposure misclassification also decreases the power to detect a positive exposure-response relationship. Although it is theoretically possible for systematic error in measuring exposure to create a spurious relationship between exposure and disease, this rarely occurs in practice and there is no evidence of such occurrence in the French study. The most likely result of measurement error in these studies is therefore underestimation of the risk associated with exposure to cobalt-tungsten carbide.

3.3 Other Limitations

The existing literature includes only two fully independent studies (Moulin *et al.* and Hogstedt and Alexandersson).

Moulin *et al.* reported that 15% of the French cohort was lost to follow-up and that most of the lost workers were foreign born. This is a minor concern: lost workers are censored at the time of loss, so the impact of loss to follow-up is not clear.

Existing human studies include only workers engaged in the production of cobalt-tungsten carbide and hard metals. There are no data on risks to end-users of hard metal products or workers reconditioning such products.

4. Other Cancer Sites

Moulin *et al.* reported non-significant elevations in risk for cancer of the pleura (SMR = 1.98) and esophagus (SMR = 1.22) and buccal cavity/pharynx (SMR = 1.20). Wild *et al.* reported additional detail on other cancers in a subgroup of the French cohort, but the findings were similar.

Non-significant elevations were found for leukemia (SMR = 2.31) and cancers of the pancreas (SMR = 1.66) and prostate (SMR = 1.62) in the Swedish cohort. There was no evidence of exposure-response for cancers of the prostate or pancreas, and the leukemias occurred primarily in lower exposure categories (Tables 5 and 7, Hogstedt and Alexandersson).

5. Overall Assessment

There is limited evidence that exposure to cobalt-tungsten carbide is associated with increased risk of lung cancer. The observed increase in risk is appreciable and there is evidence of an exposure-response gradient. In addition, there are mechanistic data consistent with cobalt-tungsten carbide acting as a human carcinogen. The association of cobalt-tungsten carbide with lung cancer is statistically significant, so chance can be reasonably excluded as an explanation. There is no evidence of confounding by smoking or other occupational exposures, but confounding cannot be entirely excluded based on the available information. The data are insufficient to support conclusions about whether the risk of lung cancer differs with exposure to unsintered versus sintered cobalt-tungsten carbide. There is insufficient evidence to link exposure to cobalt-tungsten carbide to any other cancer sites.

Other Relevant Data

1. **Toxicokinetics**

The internalized particles of cobalt-tungsten carbide are solubilized in biological fluids through complex redox reactions, including electrochemical corrosion and reactive oxygen species (ROS) generation. Thus, the particles constitute a long-term intra- and inter-cellular source of soluble cobalt and, to a much lower degree, tungsten derivatives. Most importantly, tungsten carbide facilitates the solubilization of cobalt in comparison to metallic cobalt. Tungsten is only marginally solubilized. Incubation of presintered or sintered cobalt-tungsten carbide in various biological fluids showed similar dissolution of cobalt (Stopford *et al.* 2003).

In humans exposed to cobalt-tungsten carbide dust, cobalt was found in urine, whole blood, hair, and toenails. A two-phase elimination of cobalt was observed. Longer-term models indicate that approximately 10% of ingested cobalt remains in the body with a biological half-life of 2 to 15 years. The cobalt-depleted tungsten carbide particles are retained in the human lung much longer.

The data available to date does not point at any significant differences in the toxicokinetics of cobalt-tungsten carbide among different animal species and between humans and experimental mammals. The released metals are widely distributed to many organs *in vivo*, including the brain and bone; although to a different extent (cobalt >> tungsten).

In cultured cells, tungsten carbide/cobalt solubilization yielded mainly cobalt ions, bound to biomolecules. The solubilized tungsten did not bind significantly to any plasma or tissue proteins.

2. **Genotoxicity Data**

In humans, genotoxicity of cobalt alone or cobalt-tungsten carbide has not firmly been established. In animal experiments, DNA damage and micronucleus formation were found in the lung cells of rats exposed to cobalt-tungsten carbide by intratracheal instillation. Cobalt alone also was found to be genotoxic in animals. *In vitro*, in cultured human blood lymphocytes, cobalt-tungsten carbide caused DNA damage and micronucleus formation. Other cobalt compounds also caused genotoxicity *in vitro*, and cobalt chloride inhibited DNA repair.

3. **Other Related Information: Toxicity Studies and Carcinogenicity Studies on Cobalt and Tungsten**

Cobalt alone was carcinogenic in several animal species. Immunotoxicity and chronic local inflammation was observed in man and animals. Tungstate (WO_4^{2-}) was found to promote nitrosamine-induced mammary tumors in rats. Inhalation of cobalt sulfate caused lung

tumors in rodents. Generally, cobalt-tungsten carbide dust is more toxic than cobalt or tungsten carbide dusts alone, both *in vitro* and *in vivo*.

4. **Mechanistic Data**

The mechanistic data have been derived from *in vitro* and animal experiments. The internalized cobalt-tungsten carbide particles constitute a source of ROS, soluble cobalt and tungsten species, each of which has multiple cellular targets/effects. ROS production may lead to promutagenic DNA damage (tumor initiation) and nuclear protein damage (promotion, progression). Cobalt ions produce epigenetic effects including hypoxia signaling and inhibit DNA repair that may contribute to the carcinogenic process. Cobalt sulfate has already been proclaimed by NTP as *reasonably anticipated to be a human carcinogen*. Tungsten ions were shown to be tumor promoters that may also contribute to the overall carcinogenicity of cobalt-tungsten carbide.

5. **Conclusion**

The information presented in the *Other Relevant Data* section of the draft NTP Background document on Cobalt-Tungsten Carbide Powders and Hard Metals (NTP 2008) supports the nomination of Powders and Hard Metals of Cobalt-Tungsten Carbide as *reasonably anticipated to be a human carcinogen*.

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Report Approved: _____

Max Costa, Ph.D., Chair

1-27-09

Date

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