KENNAMETAL

Listed NYSE
Kennametal Inc.

1600 Technology Way
P.O. Box 231
Latrobe, PA 15650-0231
USA
Phone: 724-539-5000
www.kennametal.com

JUL 16 2004

Transmitted Via Express Delivery

July 16, 2004

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3118
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Nomination for Possible Listing in the Report on Carcinogens: Hardmetal Manufacturing

Dear Dr. Jameson:

In the Federal Register dated Wednesday, May 19, 2004 (69 FR(97):28940-28944) the National Toxicology Program (NTP) listed 21 agents, substances, mixtures or exposure circumstances to be reviewed in 2004-2005 for possible listing in the Report on Carcinogens (ROC), Twelfth Edition. One of these nominations was for "Cobalt/Tungsten-Carbide Hard Metal Manufacturing." As the leading U.S. producer of cobalt/tungsten-carbide hardmetal powder and tools, Kennametal, Inc. (Kennametal) is enclosing our technical comments on the proposed listing of "Cobalt/Tungsten-Carbide Hard Metal Manufacturing" as a "known human carcinogen" or a "reasonably anticipated human carcinogen."

Kennametal is aware that according to NTP's "Report on Carcinogens Listing and Delisting Procedures," one of the considerations for inclusion of a substance in the ROC is information from traditional cancer epidemiology investigations. The comments attached to this correspondence specifically address this aspect of the listing and delisting procedures.

In October, 2003, the International Agency for Research on Cancer (IARC, 2003) released a monograph providing the new cancer classification for certain hardmetal compounds. Although the term hardmetal refers to a wide range of wear resistant alloys, for purposes of this letter we use the term to mean cobalt/tungsten-carbide. In its review, IARC concluded that cobalt metal with tungsten carbide was *probably carcinogenic to humans* (Group 2A) on the basis of *limited evidence* in humans for increased risk of lung cancer. Based on conversations with IARC's Dr. Yann Grosse, Kennametal is aware that the Working Group reviewed only two epidemiological studies to come to their decision regarding hardmetal. Specifically, the two studies relied upon were study published by Moulin and coworkers published in 1998, and a follow-up study published by Wild et al. in 2000.

Our comments on the nomination of "Cobalt/Tungsten-Carbide Hard Metal Manufacturing" focus on the two primary studies that were the basis of IARC's weight-of-evidence analysis. These two studies were subjected to a critical analysis using the generally accepted objective scientific method known as causation analysis. Such an

analysis is used to establish a cause and effect relationship, and is a requirement before classifying an agent, substance, mixture or exposure circumstance as to its potential to cause caner in humans.

As you will see in the attached report, the Moulin et al. (1998) and Wild et al. (2000) studies were found to be insufficient for establishing a cause and effect relationship between exposure to cobalt/tungsten-carbide and cancer. In fact, the attached analysis concludes that both of these studies were plagued by study design weaknesses (e.g., low number of deaths in the cohorts), uncertainties particularly in estimating exposure (and therefore dose), and an inability to address important confounding variables (especially for cigarette smoking). Thus, the weak associations reported by these investigators cannot be used to support the determination that cobalt/tungsten-carbide dust is a known human carcinogen. The data are simply too weak as illustrated by the causation analysis provided in the attached report. An objective evaluation demonstrates the limitations of the available epidemiological data in establishing a cause and effect relationship. Without establishing the cause and effect relationship, cobalt/tungsten-carbide dust cannot be characterized as either a "known" or "reasonably anticipated human carcinogen."

We request that NTP and the appropriate review committees consider these comments and withdrawal the nomination of cobalt/tungsten-carbide hard metal manufacturing from consideration for inclusion in the 2004-2005 ROC. If you have any questions concerning these comments please do not hesitate to contact me.

Sincerely

KENNAMETAL, INC.
[Redacted]

Dr. William Y. Hsu, Ph. D
Vice President and Chief Technical Officer

Tel (724) 539-5271
Fax (724) 539-5814
E-mail – william.hsu@kennametal.com

Enclosure

REPORT

Epidemiological Evidence for Hard Metal Carcinogenicity

Prepared for Kennametal, Inc.

Prepared by BBL, Inc.

July, 2004

BBL®
BLASLAND, BOUCK & LEE, INC.
engineers & scientists

REPORT

Epidemiological Evidence for Hard Metal Carcinogenicity

Prepared for Kennametal, Inc.

Prepared by BBL, Inc.

July, 2004

BBL®
BLASLAND, BOUCK & LEE, INC.
engineers, scientists, economists

Table of Contents

1. Executive Summary

In October, 2003, the International Agency for Research on Cancer (IARC, 2003) released a monograph providing a new cancer classification for certain hardmetal compounds and concluded that cobalt metal with tungsten carbide was "*probably carcinogenic to humans* (Group 2A) on the basis of *limited evidence* for increased risk of lung cancer." More recently, the National Toxicology Program (NTP) nominated cobalt/tungsten carbide for listing in the Report on Carcinogens, scheduled for publication in 2006, based on "recent human cancer studies on the hardmetal manufacturing industry [and] an association between exposure to hardmetals (cobalt and tungsten carbide) and lung cancer" and requested public comment on their review of cobalt/tungsten carbide hardmetal manufacturing. The "limited evidence" or "recent human cancer studies" likely underpinning both of these conclusions are the occupational epidemiological studies by Moulin et al. (1998) and Wild et al. (2000).

In this report the studies by Moulin et al. (1998) and Wild et al. (2000), two studies that address many of the same individuals and as such are not independent of one another, were subjected to causation analysis – a broadly accepted, scientifically objective methodology that utilizes a number of criteria that must be fulfilled in order to establish a causal relationship between chemical exposure and cancer. The criteria examined in this causation analysis included: 1) consistency of the association; 2) strength of the association; 3) dose (or exposure)-response relationship; 4) temporality; 5) biological plausibility; 6) confounder analysis; and 7) coherence of the evidence. A summary of the causation analysis are provided in the following Table. Application of these criteria to the aforementioned studies revealed that both studies were plagued by study design weaknesses (e.g., low number of deaths), uncertainties particularly in estimating exposure (and therefore dose), and an inability to address important confounding variables (e.g., cigarette smoking). Thus, the weak associations reported by these investigators cannot be used to support a determination that hardmetal dust is a "known or reasonably anticipated human carcinogen." Given the weak and limited nature of existing relevant data, NTP should not list hardmetal in its next scheduled Report on Carcinogens.

Causation Analysis Criteria	Criteria Met?	Explanation
Consistency of the observed association	No	• The two studies investigated the same worker population and did not represent differences in exposure, confounding factors, or other important variables. • Evidence of consistency in response among different populations, engaged in different activities, sharing exposure to a common chemical was not available within the hard metal epidemiological data.
Strength of the observed association	No	• Due to the limited number of mortalities identified and the consistent lack of statistical significance, these data could not be considered as evidence of a "precise cancer mortality."
Dose (or exposure)-response relationship	No	• Based on errors in the development of the exposure matrix and the lack of any statistically significant exposure related effects, this criteria was not met.
Temporal relationship of the observed association	No	• It was unclear whether the results associated with the population employed for 20 years or more demonstrated that the exposure appropriately preceded the observed effect and that the time interval between the exposure and the observation of the lung cancer is credible.
Biological plausibility	No	• There is insufficient evidence upon which to make a judgment as to whether or not tungsten carbide-cobalt mixtures are genotoxic to occupationally-exposed humans. • The *in vitro* and *in vivo* data are too limited, conflicting, and insufficient to support the hypothesis that the mixture of cobalt tungsten carbide is capable of transforming normal human pulmonary cells into fatal, highly malignant derivatives.
Elimination of Confounders	No	• Smoking history was inadequately accounted for and smoking is perhaps the most significant confounder for lung cancer. • A high number of workers were lost to follow-up.
Coherence of Evidence	No	• The studies failed to lay out a logical and consistent argument supporting a cause and effect relationship. • The absence of deaths from fibrosis (including Hard Metal Disease) and pneumoconiosis suggests that high exposure sufficient to cause frank lung toxicity was not present in the studied workers.

2. Introduction

In October, 2003, the International Agency for Research on Cancer (IARC, 2003) released a monograph providing the new cancer classification for certain hardmetal compounds. For purposes of this evaluation, hardmetal refers to a group of hard and wear resistant refractory composites in which hard carbide particles (in this case tungsten carbide) are bound together by a tough and ductile binder matrix (i.e., cobalt) (Lassner and Schubert, 1999). IARC concluded that "several epidemiological studies addressed cancer risks among workers exposed to dusts containing cobalt with or without tungsten carbide in hardmetal production facilities. Those conducted in France provided evidence of an increased lung cancer risk related to exposure to hardmetal dust containing cobalt and tungsten carbide, taking into account potential confounding by smoking and other occupational carcinogens. Hence, cobalt metal with tungsten carbide was evaluated as *probably carcinogenic to humans* (Group 2A) on the basis of *limited evidence* in humans for increased risk of lung cancer."

Similarly, the National Toxicology Program (NTP) recently requested public comment on their review of cobalt/tungsten carbide hardmetal manufacturing for possible listing in the Report on Carcinogens, scheduled for publication in 2006. The Report is a congressionally mandated listing of "known human carcinogens and reasonably anticipated human carcinogens" (Fed Reg. 69(97):28940). The basis for the NTP nomination of cobalt/tungsten carbide to be included in the Report is "recent human cancer studies on the hardmetal manufacturing industry [and] an association between exposure to hardmetals (cobalt and tungsten carbide) and lung cancer." Although not specified in the Federal Register announcement, these recent studies are likely the same reports relied upon by IARC to classify cobalt and tungsten carbide as a probable human carcinogen.

Although not extensively studied relative to other industrial chemicals (e.g., benzene, PCBs), there are investigations in the published scientific literature that address the association between exposure to hardmetal dust and cancer in worker populations. However, a number of these reports are of limited value in determining either an association or a cause-and-effect relationship between hardmetal dust exposure and cancer. Earlier studies on worker populations suffered from a lack of good exposure information, or a small cohort with only a limited number of deaths (e.g., Lasfargues et al., 1994; Hogstedt and Alexandersson, 1990). These factors contributed to a reduced power of the study to detect a real and significant change in cancer mortality attributable to hardmetal dust exposure.

There are two primary studies that were the focus of IARC's weight-of-evidence analysis (Grosse, Y., personal communication), as the design of the other studies resulted in reports that did not provide the statistical power to

be used in a cause and effect analysis, also referred to as a "causation analysis." The two most significant studies, the first published by Moulin and co-workers in 1998, and the second by Wild and co-workers in 2000, are actually investigations on the same group of workers. In fact, this cohort includes workers from the plant in France originally investigated by Lasfargues and co-workers and published in 1994. These two studies by Moulin et al. and Wild et al., which are assumed to be the basis of the NTP nomination, are summarized and then evaluated in terms of a causation analysis.

3. General Causation Analysis

Causation analysis is an objective scientific approach often attributed to Sir Bradford Hill who developed a set of criteria that were used in the examination of cigarette smoking and lung cancer (Hill, 1965). The "Hill Criteria" as they have come to be known have been modified over the years by various regulatory agencies (e.g., USEPA, 1999; 2003), scientific organizations, and individual scientists to objectively evaluate epidemiological data. The generally agreed upon Hill Criteria, also referred to as Causation Criteria, which are used to determine whether an observed association is causal rather than spurious, have been provided recently in the USEPA's *Draft Final Guidelines for Carcinogen Risk Assessment* (USEPA, 2003).

A causation analysis of the currently available epidemiological data for hardmetal powder was performed as summarized in subsequent sections of this report using the following seven criteria:

(1) ***Consistency of the observed association.*** Consistent findings of the same association in several if not all available studies provides the only assurance that the association exists and is not an artifact of the conditions inherent to one particular study. The reproducibility of findings constitutes one of the strongest arguments for causality (USEPA, 2003). If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.

(2) ***Strength of the observed association.*** The finding of large, precise cancer mortality increases confidence that the association is not likely due to chance, bias, or other factors. A modest change in mortality, however, does not necessarily preclude a causal association, but may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.

(3) ***Dose (or exposure)-response relationship.*** A clear dose-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests a cause and effect relationship, especially when such relationships are also observed from duration of exposure (e.g., increasing effects observed following longer exposure times). Because there are many possible reasons that an epidemiologic study may fail to detect an exposure-response relationship (for example, a small range of observed exposure levels or exposure misclassification), the absence of an exposure-response relationship does not exclude a causal relationship.

(4) Temporal relationship of the observed association. This criterion requires that exposure to the suspected causative substance appropriately precedes the observed effect and that the time interval between the exposure and the observation of the effect is credible. Because a latent period of up to 20 years or longer is associated with most cancer development, the study should consider whether exposures occurred sufficiently long ago to produce an effect at the time the cancer is assessed. This is among the strongest criteria for an inference of causality.

(5) Biological plausibility. An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of mechanistic data, however, is not a reason to reject causality.

(6) Elimination of Confounders. Confounding is the participation of other factors, including exposure to other chemicals, diet, and other socio-economic factors in the development of the observed effect (i.e., cancer). In order to develop a cause and effect relationship, the contribution of these other factors must be identified and adjustments in the analysis must be made. Adjustment for potentially confounding variables can occur either in the study design or in the statistical analysis of the results (EPA, 2003). Failure to account for confounding variables is not a reason to reject causality.

(7) Coherence of Evidence. The coherence of the evidence essentially deals with the logical consistency and believability of all of the information. An inference of causality may be strengthened by other lines of evidence (e.g., animal bioassays, pharmacokinetic studies) that support a cause-and-effect interpretation of the association. The absence of other lines of evidence is not always a reason to reject causality.

The two major epidemiological investigations of workers exposed to hardmetal dust (Wild et al., 2000; Moulin et al., 1998) were evaluated using these criteria to determine the strength of evidence for a cause and effect relationship between hardmetal dust and lung cancer. It is important to reiterate, although the publications represent two investigations into occupational exposure to hardmetal dust, they include many of the same workers. The Moulin et al. report evaluated 10 facilities, primarily in France, while the Wild et al. study focused on the largest of these facilities, and included approximately 40% of the Moulin cohort. Thus, these two studies cannot be viewed as independent investigations since they do not evaluate discrete populations; rather the lung cancer deaths in the Wild et al. reports are part of the larger mortalities included in the Moulin investigation.

4. Summary of Major Epidemiological Studies

4.1 "Lung Cancer Risk in Hardmetal Workers" by Moulin et al. (1998)

The report by Moulin and co-workers, *Lung cancer risk in hardmetal workers* (Moulin et al., 1998), is a nested case-control study conducted on workers employed for at least 3 months at 10 hardmetal facilities, from the time the factories opened until December 31, 1991. Most of the facilities were located in eastern France. The cohort consisted of 7,459 workers (5,777 males). Cases were workers who died of lung cancer; three controls were assigned for each case. Workers were followed from 1968 to 1991, and a total of 684 deaths (63 from lung cancer) were included in the analysis. Occupational exposure to hardmetal dust was assessed using a "job-exposure matrix" (JEM) that provided semi-quantitative scores for 320 job periods based on 744 air samples. The authors reported that the death rate for lung cancer (expressed as a Standard Mortality Ratio, or SMR, and 95% Confidence Intervals (95%CI)) was significantly increased (SMR = 1.30; 95%CI = 1.00-1.66). As noted by Monson (1980) if a confidence interval contains 1.0, a true mortality rate of 1.0 is possible, and suggests that the data in the study are too few to enable an unequivocal conclusion of a causal association. The odds ratios (ORs) for lung cancer mortality increased with cumulative exposure – based on the JEM. For the lowest quartile, the odds ratio (OR) equaled unity (i.e., 1.00), and with increasing exposure quartile the ORs were 2.64, 2.59, and 4.13, respectively. However, only the highest two quartiles were statistically significantly different from the lowest exposed group. There was no apparent association between death from lung cancer and duration of exposure.

When smoking was included as a co-variant in the analysis, a slight but non-significant increase in the odds ratio was detected. For nonmalignant disease, "this study failed to confirm the known pulmonary toxicity of hardmetals."

The authors concluded that this study supported the hypothesis that workers who manufacture hardmetals have an increased mortality from lung cancer due to simultaneous exposure to cobalt and tungsten carbide. However, the cohort study exhibited only a 30 percent increase in deaths from lung cancer, and this increase was "of borderline statistical significance."

4.2 "Lung Cancer Mortality in a Site Producing Hardmetals" by Wild et al. (2000)

The study conducted by Wild et al. evaluated the mortality among workers in the largest of the production sites included in the previous report by Moulin et al. (1998), a facility which had been in operation since the late 1940s. The original cohort in this study consisted of 3398 subjects, but was reduced to 2860 subjects (2216 men and 644 women) after the application of certain censoring criteria (e.g., incomplete working histories). The study population comprised all subjects who had worked at the site for at least 3 months. To quantify exposure to hardmetal dust, the Job Exposure Matrix (JEM) previously described in Moulin et al. (1998), and duration in the workshops in which the subjects worked were used in the statistical analysis. The total number of deaths from all causes by January 1, 1968 was 399. The significant findings of this study include:

- A weak association was found between exposure to hardmetal dust and smoking (i.e., individuals exposed to hardmetal dust were more likely to be smokers).
- In the entire cohort, without regard to job classification, a significant increase in mortality from lung cancer was observed in men (SMR = 1.70; 95% CI 1.26 – 2.26), but not in women.
- Among workers involved in hardmetal production, without the distinction of sintering or not, a statistical increase in mortality from lung cancer was observed (SMR of 1.93; 95% CI 1.05 – 3.23).
- Consistently high SMRs were found among workers ever involved in (SMR = 2.42; 95% CI 1.10 – 4.59) and only employed in (SMR = 2.91; 95% CI 1.06 – 6.34) hardmetal production steps before sintering.
- All exposures to chemicals considered by IARC as carcinogens resulted in a significant increase in mortality due to lung cancer (SMR = 2.56; 95% CI 1.28 – 4.59).
- Workers engaged in maintenance activities (only or ever), with non-quantifiable exposures to hardmetal dust, had consistently elevated SMRs for lung cancer. "These increased risks are difficult to interpret as several possible carcinogenic exposures had been coded by the experts who developed the JEM."

The authors concluded that an excess mortality from lung cancer was found among workers producing hardmetals and maintenance workers, which cannot be attributed to smoking alone. The excess appears mostly in subjects exposed to unsintered hardmetal dust.

5. Causation Analysis of Major Hardmetal Studies

The study of Moulin et al. and Wild et al. were subjected to a formal causation analysis using the seven causation criteria previously described. Although each study was independently evaluated in this manner, it is important to remember that the two studies actually addressed many of the same individuals. That is, the individual comprising the Wild cohort were also a significant proportion of the Moulin cohort. Therefore Wild et al. represents, to some degree, a re-evaluation or update of the Moulin report, and is not a distinctive, diverse report. Thus, it would not be unexpected that there could be similar findings between the two reports. Acknowledging this limitation in the available data is an important consideration as the studies are evaluated in a formal causation analysis.

Consistency of the observed association

Consistent findings of the same association in several if not all available studies provides the only assurance that the association exists and is not an artifact of the conditions inherent to one particular study. Unfortunately, as previously mentioned, the Moulin study, along with Wild et al. (2000), provide the only investigations with study designs generating the statistical power to detect a true increase in cancer mortality. As these two studies investigated the same worker population and therefore do not represent differences in exposure, confounding factors, or other important variables, there are too few additional available studies to satisfy the criterion of consistency.

Other studies on hardmetal workers have been published in the scientific literature, and their results would appear to support the findings reported in the study by Moulin et al. However, these reports are of limited utility in demonstrating consistency in the observed association because of the limited power of the studies. For example, as cited in Moulin et al. (1998), the report by Hogstedt and Alexandersson (1990) on hardmetal workers in Swedish factories reported a similar 30% increase in lung cancer among its workers (SMR = 1.34), but it dealt with only 17 lung cancer deaths. The only other mortality study of hardmetal workers, Lasfargues et al. (1994), was a preliminary investigation of the facility included in both the Moulin et al. and Wild et al. reports. Lasfargues and co-workers identified an increase in mortality attributed to lung cancer among workers exposed to hardmetal dust (SMR = 2.13; 95% CI 1.02 – 3.93). However, these investigators also stated: "because of the small numbers involved, no firm conclusion should be drawn from this study."

Because three of the four studies on hardmetal workers, including the two largest investigations, consider the same worker population, there is no way of demonstrating that the weak finding of an increased risk for

mortality from lung cancer is not an artifact of the conditions inherent to one particular study. Typically, chemicals designated as "known human carcinogens" have been investigated in many different cohorts often from several different countries, and in all of these studies a consistent finding was reported. For example, benzene exposure and its link to cancer has been investigated in workers not only from different facilities, but also engaged in different industries. Evidence of cancer has been obtained from studies on workers in the rubber, petrochemical, and pliofilm production industries (Budinsky et al., 1999). It is this consistency in response among different populations, engaged in different activities, sharing exposure to a common chemical, that provide the evidence in support of a cause and effect relationship. This evidence is not available within the hardmetal epidemiological data, and therefore the criterion of consistency has not been satisfied.

Also, the criterion of consistency deals with uniformity in the nature of the response, including the type of cancers reported in the study. In both the Moulin et al. and the Wild et al. studies, "cases" were defined simply as "the cohort workers who had died of lung cancer" while the report did not specify as to the type of lung cancer (cell type and specific tissue involved). Thus, it appears any and all cancers of the lung were grouped together, although specificity of tumor type in the lung is known to be related to the causative agent. For example, cigarette smoking has been shown to be more commonly associated to squamous-cell and small-cell carcinomas and not adenocarcinomas (IARC, 1986). Likewise, vinyl chloride is specifically associated with angiosarcoma (EPA, 2003). Based on the generality of this grouping, one cannot determine if all of the "lung cancers" observed either within a particular study, or between the two reviewed studies, demonstrated a consistent biological response.

Strength of the observed association

In the Moulin cohort, there was only a 30 percent increase in deaths from lung cancer. Not only was this increase only borderline statistically significant, but it hardly qualifies as a "large, precise cancer mortality." Also, a standard mortality ratio of less than 2.0 has been viewed by scientists and federal and state courts (Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F. 3rd 1311; 9th Cir. 1995) as insufficient to demonstrate that a particular illness or condition was more likely than not caused by the toxic agent (Norris et al., 2004).

The entire male cohort in the study conducted by Wild and co-workers exhibited an increase in lung cancer, although like the Moulin study, there was less than a 2-fold increase (SMR = 1.70; 95% CI 1.24 – 2.26). When the cohort was further segregated into subcategories of exposure (e.g., only employed in production before sintering), the SMRs increased slightly, although the number of deaths attributed to the particular category was

always less than 10, and none of the elevated SMRs reached statistical significance with the exception of co-exposure to "IARC carcinogens."

The questionable significance of SMRs of less than two, as reported for hardmetal exposure and lung cancer, was addressed in an article by Taubes (1995). When one considers the uncertainties associated with accurately characterizing exposures, biological plausibility, and addressing confounding and sampling bias, many epidemiologists insist that no single epidemiological study is pervasive unless there is a three- to four-fold risk increase. Since the Wild cohort is only a subset of the Moulin cohort, some of the biases, measurement errors, and confounding factors are identical, and to some degree cannot be viewed as independent studies. As such, to satisfy the criterion of strength of association, these investigations need to demonstrate risks higher than those reported in either study.

Given the limited number of mortalities identified in these categories, and the consistent lack of statistical significance, these data could not be considered as evidence of a "precise cancer mortality," and therefore the criterion of "strength of the association" has not been satisfied.

Dose (or exposure)-response relationship

As there were no measurements that could be used to develop an estimate of a dose (e.g., biomarker data such as blood or urine) or even actual exposure (e.g., personal air monitor data), a surrogate for exposure was developed by the investigators. A "job-exposure matrix" (JEM) was developed by a committee of 9 experts, and assigned semiquantitative estimates of exposure to cobalt and tungsten carbide based on 320 job periods. In addition, atmospheric concentrations of cobalt were available from previous studies and were used in an attempt to validate the matrix.

Use of the empirical data illustrate that the JEM was not successful in discriminating exposure conditions, and therefore cannot be used to establish a dose-response effect. The following table is a reproduction of Table 1 from the Moulin et al. report.

JEM Level Compared to Measured Cobalt Air Concentrations

JEM Level	# of Samples	Arithmetic Mean ($\mu g/m^3$)	Minimum ($\mu g/m^3$)	Maximum ($\mu g/m^3$)	Geometric Mean ($\mu g/m^3$)
1	0				
2	70	39.37	1	228	20.04
3	59	63.38	0.5	449	18.25
4	98	62.33	2	465	26.41
5	32	87.91	1	515	28.59
6	**2**	169.00	134	204	165.34
7	**3**	102.33	34	155	85.36
>7 (8 and 9)	**0**	**No Data**			

There are a number of interesting insights into the exposure characterization of this cohort that are observed from these data:

1) Although an increase in the JEM score was supposed to represent an increase in exposure, for the arithmetic mean and the geometric mean there is little difference in exposures across JEM 2 through 5. As noted by USEPA (1989; 1992) an average concentration is the most appropriate matrix for evaluating cancer risks because cancer is a response to a chronic exposure and the average concentration is most representative of the concentration experienced over time.
2) The arithmetic mean and geometric mean personal air data for JEM #7 are *lower* than JEM #6; these values are based on only 3 and 2 samples, respectively.
3) No analyses were performed on these data to establish that they were statistically different from each other.
4) For the maximum air concentrations, it can be seen that JEM #6 and #7 are much *lower* than JEM #3, #4, and #5. This is in conflict with the claim that JEMs #6 and #7 represent higher exposure categories than JEM #3, #4, and #5.
5) For JEM exposure categories #8 and #9 (the two highest categories) there were no exposure data.

Another interesting, and potentially disconcerting, issue involving the exposure estimate is that the earliest exposure data were from 1971, whereas the first two factories evaluated in this study opened in 1942 and 1945. Hence, earlier exposure levels for many of the cancer cases were not included; more than 93% of the cancer cases were hired before 1970.

Perhaps reflective of the lack of an adequate exposure characterization of the worker population, the authors were unable to demonstrate an exposure related effect. In fact, the only "exposure levels" with a statistically significant elevated lung cancer mortality were observed in the lowest exposure grouping, levels 2 and 3 (OR = 3.37; 95% CI 1.19 – 9.56). The ORs for lung cancer in all other groupings based on JEM levels (i.e., 4-5, and 6-9) were not significantly elevated, and the exposure-related trend analysis also was not statistically significant. Thus, based on the errors in the development of the exposure matrix, and the lack of any statistically significant exposure related effects (which may be a function of the flawed JEM) the results do not satisfy the criterion of demonstrating a dose-response relationship.

Temporal relationship of the observed association

Cancer from occupational exposures typically has a latency period of approximately 20 years (USEPA, 2003). In the event that a chemical causes cancer, longer intervals between first exposure (start of employment) result in a larger number of exposure-related cancer cases. This is because chemically induced cancer takes time to develop and be observed (diagnosed and/or death). This is particularly true for lung cancer. Therefore, we should observe an increase in the SMRs as time since first exposure increase above 20 years. In this cohort, 33% of the lung cancer deaths (20 of 61) occurred before the individuals had reached 20 years since the start of employment (and presumably the initiation of exposure to hardmetal). For this sector of the cohort, temporality seems not to be satisfied. The SMRs for lung cancer mortality in groups employed for 20 to 29 years and greater than 30 years were elevated (1.42 and 1.25, respectively), although the authors did not provide the data to determine if this moderate elevation was statistically significant. Also, there was no increase in the SMR with increasing time since first exposure, and as shown in the table below, the SMRs remain relatively constant over time. As such, it is unclear whether the results associated with the population employed for 20 years or more demonstrate that the exposure appropriately preceded the observed effect, and that the time interval between the exposure and the observation of the lung cancer is credible. Thus, it appears that temporality was not satisfied in this study.

Latency (time since first employment)	SMR for Lung Cancer
0-9	0.74
10-19	1.33
20-29	1.42
> 30	1.25

Biological plausibility

The likelihood of a causal association between exposure to a substance and an adverse health outcome is strengthened if there exists a biologically plausible mechanism, firmly grounded in science, to explain how the substance leads to the initiation and/or progression of disease. In the case of colbalt-tungsten carbide mixtures, genotoxicity has been advanced and investigated as a possible mechanism by which hardmetals may cause cancer in humans. However, given the inconsistent results observed between *in vitro* and *in vivo* experimental studies, together with the lack of a genotoxic effect in workers exposed occupationally to cobalt or colbalt-tungsten carbide powders, it is not clear whether colbalt-tungsten carbide mixtures are in fact genotoxic to humans at levels encountered in the workplace.

Genotoxicity of colbalt-tungsten carbide mixtures has been assessed *in vitro* in human lymphocytes using alkaline elution, comet, and micronucleus assays (Anard et al., 1997; Van Goethem et al., 1997; DeBoeck et al., 1998; DeBoeck et al., 2003a). Under the conditions employed, colbalt-tungsten carbide mixtures were found to be clastogenic. However, the result of these studies must be viewed cautiously, for several reasons. First, the cells used in these studies were collected from a very small population of humans. For example, in the study by DeBoeck et al. (1998) lymphocytes were collected from three healthy, non-smoking females who were less than 30 years of age. Van Goethem et al. collected cells from one human (sex not specified) who was less than 30 years of age while DeBoeck et al. (2003) collected cells from only two individuals, one male and one female, who were both reportedly less than 28 years of age. Anard et al. (1997) don't specify from how many individuals cells were collected. Given the few individuals employed, the results of these studies must be viewed as preliminary.

Secondly, in most of these studies there was a substantial inter-experimental and inter-donor variability, casting some doubt as to the interpretation of the results. Indeed, DeBoeck et al. (2003a) noted that since substantial inter-experimental and inter-donor variation was observed in their study "the current data need to be considered as preliminary." And finally, the cells used in these experiments were obtained from peripheral blood and not from the lung, the latter of which is suspected as the target of carcinogenicity of colbalt-tungsten carbide mixtures. Whether or not cells from the lungs, such as type II pneumocytes, would respond similarly has not been investigated. Thus, these studies do not provide evidence of genotoxicity in cells of the lungs.

In comparison to *in vitro* studies, an *in vivo* study using rats yielded mixed results (DeBoeck et al., 2003b). In this study male Wistar rats received intratracheal doses of a colbalt-tungsten carbide mixture after which various

cells were collected (type II pneumocytes, bronchoalveolar lavage cells, and lymphocytes) and subjected to alkaline comet or micronucleus assays. With the exception of the *ex vivo* micronucleus test result using type II pneumocytes and the alkaline comet assay result using type II pneumocytes (this latter finding was judged to be negative by DeBoeck et al., 2003c) all other assays results were negative. Given the varied findings in this study - not to mention the questionable finding in the alkaline comet assay with type II pneumocytes - it is not at all clear whether the colbalt-tungsten carbide mixture used in this study caused a clastogenic response.

In the sole human study designed to examine the genotoxic effects of exposure to colbalt-tungsten carbide dusts (as well as cobalt dusts) in workers, negative results were reported (DeBoeck et al., 2000). Thus, in workers occupationally exposed to low levels of cobalt-tungsten carbide dust, no genotoxic effect was observed.

These studies have been used to advance a biologically plausible mechanism for genotoxicity mediated by the generation of reactive oxygen species that randomly attach and fragment DNA, as detected in these *in vitro* tests. However, for more than a decade, scientists have realized that a positive outcome in short-term, *in vitro* tests does not demonstrate a biologically plausible link to cancer in humans.

Several years ago, scientists from the National Institute of Environmental Health Sciences engaged in an extensive review of the *in vivo* and *in vitro* data available on 77 chemicals studied as part of the National Cancer Institute and the National Toxicology Program (Tennant et al., 1991). The purpose of this assessment was to provide "a thorough evaluation of the ability of these [*in vitro*] tests to predict rodent carcinogenicity." [Note that these authors are not even addressing the issue of extrapolating animal studies to human response.] The conclusions reached by the panel of researchers clearly highlight the uncertainty associated with the information obtained from these types of studies and concluding a mechanistic link to cancer. While arguably consistent with the thinking in the 1970s, this direct extrapolation is no longer reliable based on today's body of scientific knowledge. These scientists stated:

> *The standard against which the performance of STTs [short-term tests] is measured has changed dramatically in the past decade. The high level of concordance [between in vitro results and carcinogenicity] published in the early 1970s were accurate at the time. Nearly all known carcinogens tested were genotoxic, . . .*
>
> *For more than a decade, the dominant paradigm motivating the use of STTs to predict chemical carcinogenesis has been that carcinogens are mutagens and, by implication, that mutagens are carcinogens. On the basis of the results presented here, it is clear that strong qualifications to these associations are needed. No single in vitro STT adequately anticipates the diverse*

> *mechanisms of carcinogenesis; and more important, the advantage of a battery of in vitro STTs is not supported by results of the present study.*
>
> *It is clear that even with a battery of assays, not all rodent carcinogens are in vitro mutagens nor are all in vitro mutagens rodent carcinogens. If current in vitro STTs are expected to replace long-term rodent studies for the identification of chemical carcinogens, then that expectation should be abandoned.* [emphasis added]

Thus, this single effect (i.e., direct damage to cellular DNA) alone does not explain the development of cancer in humans. As recently described in great detail by Hanahan and Weinberg (2000), tumorgenesis in humans is a multistep process with several rate-limiting, stochastic events that are critical to the progressive transformation of a normal human cell into highly malignant derivatives. As a caution to over-interpreting the results of *in vitro* studies, the authors noted:

> *By simplifying the nature of cancer — portraying it as a cell-autonomous process intrinsic to the cancer cell — these experimental models have turned their back on a central biological reality of tumor formation in vivo: cancer development depends upon changes in the heterotypic interactions between incipient tumor cells and their normal neighbors.*

Overall, there is insufficient evidence upon which to make a judgment as to whether or not colbalt-tungsten carbide mixtures are genotoxic to occupationally-exposed humans.

The limited experimental evidence obtained from studies on the impact of oxygen radicals on cellular DNA may provide some initial insight into a possible mechanism of chemical carcinogenesis. These data, however, are too limited, conflicting, and insufficient to support the hypothesis that the mixture of cobalt tungsten carbide is capable of transforming normal human pulmonary cells into fatal, highly malignant derivatives. This purported mechanism has not been conclusively confirmed and remains only a hypothesis. As such, the criterion of biological plausibility has not been fulfilled.

Elimination of Confounders

Smoking is perhaps the most significant "confounder" for lung cancer. Unfortunately, the authors of this study inadequately accounted for smoking history. Perhaps as evidence of this flaw, the OR for lung cancer associated with smoking was only 3.38. This is significantly lower than the OR typically reported for deaths associated with smoking (see Hill, 1965 and IARC, 1986). The authors acknowledged that such a low risk associated with smoking may be due to misclassification. Other inadequacies in addressing smoking as a confounding variable include:

1) None of the 61 cancer cases were actually interviewed for smoking histories.

2) No medical records were reviewed for independent confirmation of self-reported or proxy-reported smoking histories.
3) 70.5% (43 cancer cases) of the smoking history was obtained from colleagues.
4) 11.5% (7 cancer cases) of the smoking history was obtained from relatives.
5) 18% (11 cancer cases) had **no** information on smoking.

Without accounting for perhaps the most important confounder for lung cancer, these authors cannot make any determination regarding the cause-and-effect relationship, or even the association, between hardmetal exposure and lung cancer.

In addition to the problems with accurately characterizing the most important confounding variable for lung cancer, an unacceptably high number of workers were lost to follow-up. Over 15% of the exposed population was not accounted for in this study (1,131 workers). Inclusion of these workers undoubtedly would have changed the reported findings of the study – they might have increased or decreased the SMR. In any event, this rendered the study uninterpretable, and the authors should not have completed the study until these workers were found.

Inadequate evaluation of cigarette smoking as a confounder for lung cancer also plagued the Wild et al. report. The following paragraph taken from the published report highlights the uncertainty in the assessment of the possible contribution to lung cancer from smoking:

> *Exposure to smoking was abstracted from the records of the occupational health department; however, the information was sketchy until 1978, when current smoking or non-smoking was recorded but no mention was made of past smoking. Therefore, this information was reassessed by a volunteer group of former workers.*

This indicates that quantitative information on smoking histories was unavailable until 1978, which is almost 30 years after the initiation date for exposure considered in the study – January, 1950. Even after the improvement in record keeping, the use of "a volunteer group of former workers" to obtain historical information was likely inadequate, although the authors did not provide any critical analysis of effectiveness of this approach.

A careful review of the two major studies clearly indicates that neither of the investigation teams adequately addressed the most significant confounding variable in studies of lung cancer in human populations – cigarette smoking. Because the smoking histories were not quantitatively defined in the populations of workers, there is

no way of knowing the contribution of this known cause of lung cancer on the observed results. This is especially troubling given the low number of deaths contained in the studies (especially in Wild et al.), and the relatively low SMRs reported for lung cancer. Only a few cases misclassified as to their smoking status would have a dramatic impact on the interpretation of a casual relationship between hardmetal exposure and lung cancer. Thus, neither of these studies satisfied the confounding criterion.

Coherence of Evidence

As previously stated, the limited and conflicting data available from *in vitro* and *in vivo* studies do not provide a scientifically grounded biologically plausible mechanism supporting a cause-and-effect interpretation of the purported association between occupational exposure to colbalt-tungsten carbide mixtures and lung cancer. Additional evidence contained in the two major epidemiological studies also lead to challenges of the consistency of the body of scientific evidence.

Generation of reactive oxygen species lead to cell damage and structural changes in the lung. The types of pulmonary changes expected from the biochemical reactions initiated by oxygen radicals would include fibrotic changes (Lison and Lauwerys, 1992). This sort of insult has been observed in Hardmetal Disease. Thus, one would expect evidence in the epidemiological studies if this biochemical mechanism was possibly involved in the etiology of cancer in hardmetal workers.

However, Moulin et al. stated "this study failed to confirm the known pulmonary toxicity of hardmetals." The absence of deaths from fibrosis (including Hardmetal Disease) and pneumoconiosis suggests that high exposure sufficient to cause frank lung toxicity was not present in these workers. The following are mortality incidence from the Moulin cohort:

<u>For Pneumoconiosis:</u>

Men - 3 Observed versus 2.25 Expected
Women – No deaths were observed

<u>For Fibrosis</u>

Men – 0 Observed versus 0.62 expected
Women – No deaths were observed.

Similar findings were reported by Wild and co-workers:

<u>For Pneumoconiosis:</u>

Men - 1 Observed versus 0.55 Expected
Women – No deaths were observed

For Fibrosis
Men – 0 Observed versus 0.27 expected
Women – No deaths were observed.

These data do not identify the *incidence* of either fibrosis or pneumoconiosis with the populations, and therefore do not provide a complete picture of lung injury in either the exposed or unexposed populations. However, one would expect that if the incidence of either disease was significantly elevated, it would be reflected in increased mortality from the injury. This was not observed. This additional information, used in concert with the epidemiological and experimental data, fails to lay out a logical and consistent argument supporting a cause and effect relationship. Thus, the body of scientific information fails to satisfy the criterion of Coherence

6. Summary

In October, 2003, the International Agency for Research on Cancer (IARC, 2003) released a monograph providing the new cancer classification for hardmetal. The Agency concluded that several epidemiological studies conducted in France provided evidence of an increased lung cancer risk related to exposure to hardmetal dust containing cobalt and tungsten carbide. As a result of their analysis, IARC characterized cobalt metal with tungsten carbide as *probably carcinogenic to humans* (Group 2A) on the basis of *limited evidence* in humans for increased risk of lung cancer. Similarly, the National Toxicology Program (NTP) recently requested public comment on their review of cobalt/tungsten carbide hardmetal manufacturing for possible listing as a "known human carcinogens and reasonably anticipated human carcinogens" based on the available epidemiological evidence.

In order for a compound to be categorized as a known or probable human carcinogen, the available data must demonstrate a cause and effect relationship. There is a broadly accepted, scientifically objective, methodology available to evaluate these data and establish this causal relationship between chemical exposure and cancer. This methodology, referred to as a causation analysis, was used to evaluate the two major epidemiological studies on hardmetal exposure and lung cancer, the reports by Moulin and co-workers, published in 1998, and the investigation by Wild et al., published in 2000.

These studies were plagued by study design weaknesses (e.g., low number of deaths in the cohorts), uncertainties particularly in estimating exposure (and therefore dose), and an inability to address important confounding variables (especially for cigarette smoking). Thus, the weak associations reported by these investigators cannot be used to support the determination that hardmetal dust is a known human carcinogen. The data are simply too weak, and as illustrated by the causation analysis provided in this section, an objective evaluation of these reports demonstrates the limitations of the available epidemiological data in establishing a cause and effect relationship. Without establishing the cause and effect relationship, hardmetal dust cannot be characterized as either a "known" or "probable human carcinogen."

7. References

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

Budinsky, R., R. DeMott, M. Wernke, and J. Schell. 1999. An evaluation of modeled benzene exposure and dose estimates published in the Chinese-National Cancer Institute collaborative epidemiology studies. Regul. Toxicol. Pharmacol. 30:244-58.

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

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

DeBoeck, M., M. Kirsch-Volders, and D. Lison. 2003c. Cobalt and antimony: genotoxicity and carcinogenicity. *Mutation Research* 533:135-152.

DeBoeck, M., S. Lardau, J.P. Buchet, M. Kirsch-Volders, and D. Lison. 2000. Absence of Significant Genotoxicity in Lymphocytes and Urine from Workers Exposed to Moderate Levels of Cobalt-Containing Dust: A Cross-Sectional Study. *Environmental and Molecular Mutagenesis* 36:151-160.

DeBoeck, M., D. Lison, and M. Kirsch-Volders. 1998. Evaluation of the *in vitro* direct and indirect genotoxic effects of cobalt compounds using the alkaline comet assay, Influence of interdonor and interexperimental variability. Carcinogenesis 19(11):2021-2029.

Hill, A. 1965. The environment and disease: Association or causation?: Proc. R. Soc. Med. 58:295-300.

Hogstedt, C., Alexandersson R. 1990. Mortality among hard metal workers. Arbetsmiljèoinstitutet, Fèorlagstjèanst, 171 84 Solna, Sweden. 26p. 25 ref.

IARC 2003. Monographs on the Evaluation of Carcinogenic Risks to Humans. Cobalt in Hard-metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide 86, 7-14.

IARC 1986. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Tobacco Smoking Vol. 38. Lyon, France.

Lasfargues, G., P. Wild, J. Moulin, B. Hammon, B. Rosmorduc, C. Rondeau du Noyer, M. Lavandier and J. Moline. 1994. Lung cancer mortality in a French cohort of hard-metal workers. Am. J. Ind. Med.. 26(5):585-95.

Lasner, E. and W. Schubert. 1999. Tungsten: Properties, Chemistry, Technology of the Element, Alloys and Chemical Compounds. Kluwer Academic / Plenum Publishers, New York.

Lison D., R. Lauwerys. 1992. Study of the mechanism responsible for the elective toxicity of tungsten carbide-cobalt powder toward macrophages. Toxicol. Lett. 60(2):203-10.

Monson, R. 1980. The Interpretation of Epidemiologic Data. In *Occupational Epidemiology.* 93-103p.

Moulin, J., P. Wild, S. Romazini, G. Lasfargues, A. Peltier, C. Bozec, P. Deguerry, F. Pellet and A. Perdrix. 1998. Lung cancer risk in hard-metal workers. Am. J. Epidemiol. 148, (3):241-8.

Norris, A., S. Blitch and T. Yoo. 2004. Manganese-Induced Neurologic Injury: The Welding Industry Position. Mealey's Litigation Update: Welding Rods. 29-34p.

Taubes, G. 1995. Epidemiology faces its limits: Science 269:164-169.

Tennant, R. 1991. The genetic toxicity database of the National Toxicology Program: Evaluation of the relationships between genetic toxicity and carcinogenicity: Environ. Health Perspect. 96:47-51.

USEPA (United States Environmental Protection Agency). Draft Final Guidelines for Carcinogen Risk Assessment. Washington, DC: USEPA; 2003. EPA/630/P-03/001A.

USEPA (United States Environmental Protection Agency). Office of Research and Development. Risk Assessment Forum. Guidelines for carcinogen risk assessment , Review Draft. Washington, D.C.: USEPA. 1999 NCEA-F-0644.

USEPA (United States Environmental Protection Agency). Environmental Protection Agency. Guidelines for Exposure Assessment; Notice. 1992. Federal Register 57(104).

USEPA (United States Environmental Protection Agency). Risk Assessment Forum. Workshop report on EPA guidelines for carcinogen risk assessment. Washington, D.C.: USEPA. 1989. EPA/625/3-89/015.

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

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