

## APPENDIX 3

### ***Summary of animal studies relevant for carcinogenicity***

#### *Groth et al. (1980)*

Be metal, BeAl alloy, passivated Be metal, and Be(OH)<sub>2</sub> were demonstrated to be pulmonary carcinogens in rats. These findings are supported by successful transplantation experiments. In addition, other alloys of Be, VBe<sub>12</sub>, TiBe<sub>12</sub>, TaBe<sub>12</sub>, NbBe<sub>12</sub>, and Be<sub>4</sub>B were found to produce pulmonary metaplasia, frequently a preneoplastic lesion in rats. Old rats were shown to be more susceptible to the induction of pulmonary metaplasia than young adult rats. These results indicate that a lower dose of Be would be required to produce cancer in old animals compared to young ones. A discussion on the lung cancer incidence in Be production workers is included.

#### *Finch et al. (1996)*

This publication is primarily a summary of studies already evaluated for the purpose of this statement. No conflicting conclusions were reached.

#### *Belinsky et al. (1994)*

This abstract only reported on preliminary findings. Alterations in the p53 gene were studied in F344/N rats exposed to beryllium and other compounds (carbon black, diesel exhaust, X-rays). The alterations were determined by immunohistochemistry, direct sequencing and single strand conformation polymorphism (SSCP) analysis. Immunohistochemistry did not reveal an increase in p53 protein levels in either of the exposure groups. No other findings relevant to beryllium exposure were reported.

#### *Nickel-Brady et al. (1994)*

Single inhalation exposure of Fisher 344 rats to Be metal led to a 64% lung tumour incidence after 14 months. The induced carcinomas were examined for genetic alterations in the K-ras, p53, and c-raf-1 genes. No K-ras codon 12, 13 or 61 mutations were detected in 24 lung tumours by direct sequencing, but a more sensitive method detected 2/12 GGT-GTT transversions, considered to be a rare and late event. Mutant p53 nuclear immunoreactivity was observed in any Be-induced tumour, and mutations were detected within exons 5 - 8 of the p53 gene. No rearrangement of the raf-1 protooncogene was detected by Southern blot analysis. The results indicate that the mechanism underlying the development of Be-induced lung cancer in rats does not involve gene dysfunctions commonly associated with human non-small-cell lung cancer.

#### *Belinsky et al. (1997)*

Pulmonary adenocarcinomas or squamous cell carcinomas were induced by beryllium metal. In these tumours, mutation of the K-ras gene was determined by approaches that included DNA transfection, direct sequencing, mismatch hybridization and restriction fragment length polymorphism analysis. K-ras activation in Be-induced lung tumours had a low incidence of 2/24 and consisted of a GGT → GTT transversion. Alteration in the p53 gene was assessed by immunohistochemical analysis for p53 protein and single strand conformation polymorphism (SSCP) analysis of exons 4 to 9. None of the adenocarcinomas was immunoreactive toward the anti-p53 antibody CM1. The squamous cell carcinomas induced by beryllium were available for investigation.

*Finch et al. (1994)*

An equal number of male and female F344/N rats (n= 936) were exposed to Be metal (MMAD= 1.4  $\mu$ M) by nose only acute inhalation. The following lung burdens were achieved: 33, 84, and 420  $\mu$ g. Additional control animals were sham-exposed only. Mortality was 33% and 64% (male and female, respectively) in the 420  $\mu$ g group within 3 weeks of exposure. The incidence of lung tumours (animals surviving until day 365) was 2%, 62%, 89%, and 89% (males) and 0%, 83%, 96%, and 100% (females) for the control group, 33, 84 and 420  $\mu$ g dose groups. The most common primary malignant lung neoplasms were adenocarcinomas, followed by squamous cell carcinomas and adenosquamous carcinomas.

*Litvinov et al. (1983)*

The study part dealing with beryllium metal is reported only in words without any experimental details. Therefore, only an executive summary can be provided. Albino mongrel rats of 140-150 g were treated by single intratracheal administration of beryllium metal. Two particle size ranges of the material were tested: big and fine particles. Doses were 0.5-18 mg/kg. While little effect was seen with the large particles, dose-dependent neoplastic effects in lung were described after administration of fine particles.

*Finch et al. (1995)*

F344 rats and C3H or A/J mice were exposed per nasally to single doses of inhalable Be metal at comparable lung burdens. Rats developed chronic pulmonary infiltration, hyperplasia of alveolar epithelium and retarded clearance of radiolabeled tracer particles at lower lung burdens and had a substantial neoplastic response. Mice showed no or minimal neoplastic response only.

*Finch et al. (1998)*

Mice were exposed by inhalation once to a lung clearance marker ( $^{85}\text{Sr}$ -FAP) followed by a single exposure to metallic beryllium at Be-burdens of 0, 1.7, 2.6, 12 and 34  $\mu$ g per mouse and followed up for 350 days. Investigated parameters were lung clearance of the marker and beryllium, lung pathology (macro- & micropathology, bronchoalveolar lavage analyses). Lung weights were increased at the 12 and 34  $\mu$ g burdens, at these levels there was also a clear retardation of clearance of the  $^{85}\text{Sr}$ -FAP marker and of beryllium. Some cellular BALF were occasionally increased in the higher burdens. While the 1.7  $\mu$ g was practically without adverse effect, minor pathology findings were noted at 2.6  $\mu$ g. At the burdens of 12 and 34  $\mu$ g granulomatous pneumonia, lymphocytic interstitial aggregates and mononuclear infiltrates occurred with high incidence. Comparing effects and lung burdens, mice seem to be less sensitive to inhalatory Be effects than rats.

*Finch et al. (1998)*

Heterozygous TSG-p53 knockout mice (p53<sup>+/-</sup>, each 15 male and 15 females/group) were exposed to Beryllium metal powder (MMAD 1.8  $\mu$ m) for either 112 min. at 34  $\mu$ g Be/l air (target initial lung burden of 15  $\mu$ g Be), or for three consecutive days (139 min./d at 36  $\mu$ g Be/l air). Concurrent controls (15m/15f) were exposed to filtered air (sham). The same experiment was conducted in parallel with wild-type mice (p53<sup>+/+</sup>). In this experiment, 3 satellite animals per exposure condition were added and were killed after 7 days to determine the initial lung burden. 4-5 mice/group were sacrificed 6 months after exposure, and remaining animals were sacrificed when moribund (the rest of the

population when 90% mortality was reached). Increased numbers of neoplasm were found in p53 knockout mice, while no neoplasms were observed in wild-type mice.

*Nikula et al. (1995)*

The pulmonary carcinogenicity of Be metal was compared in A/J (sensitive to lung tumours) and C3H/HeJ (resistant to lung tumours) mice. Female, 6-8 week old mice (206 each strain) were exposed once, nose only, to Be metal or to filtered air (controls, 50 each strain). Despite simultaneous exposure of both strains, Be initial lung burdens (ILTs/g body weight) were 63 mcg (3.4 mcg/g) for C3H/HeJ mice and 47 mcg (3.0 mcg/g) for A/J mice. Clearance half-times were 108 and 97 days for C3H/HeJ and A/J mice, respectively. Differences between strains in ILBs and clearance half-times were statistically significant. Be exposure reduced survival significantly for C3H/HeJ mice and marginally for A/J mice. There was no difference in tumour incidence, multiplicity, or latency in Be-exposed C3H/HeJ mice compared to controls. When mice sacrificed before 11 months on study were excluded (sacrifices to determine ILBs and study preneoplastic lesions), the incidence of lung neoplasia from 11 to 22 months was slightly increased in Be-exposed A/J mice. Six percent of control and 19% of Be-exposed A/J mice had more than one neoplasm. Analyses of K-ras mutation patterns in neoplasms from exposed and control A/J mice suggest that the increased multiplicity was due to promotion of spontaneously initiated cells. Further analyses will define whether these increases are statistically significant and if tumour latency was decreased.

*Schepers et al. (1961)*

The study parts dealing with beryllium metal is reported only in a table in the publication without further details. Therefore, a full summary can not be provided. No neoplasms were observed in guinea pigs three months after a single intratracheal instillation of 75 mg beryllium metal.

## APPENDIX 4

### ***Early Cohort studies on Workers Employed at the Beryllium Processing Plants at Lorain (Ohio) and Reading (Pennsylvania).***

#### *Studies by Mancuso*

The retrospective cohort studies at the beryllium processing plants at Lorain (Ohio) and Reading (Pennsylvania) were initially conducted on 3685 male workers and extended in several follow-up studies. A significant increase in the mortality by lung cancer was reported in workers with a lagging of more than 15 years since the beginning of their employment (Mancuso and El Attar 1969; Mancuso 1970; Mancuso 1979; Mancuso 1980). However, these studies are characterized by a lack of exposure data, lack of consideration of confounding factors such as smoker status and other possible lung carcinogens that may occur at work places in metal processing plants. Uncertainties about the national mortality rates during the years 1968-1975 were an additional limiting factor 1. Furthermore, mortality rates of lung cancer among the workers could not be shown to be correlated with the duration of employment when dividing the cohort in short (less than 12 months; SMR 1.38,  $p < 0.05$ ) medium (12 up to 48 months; SMR 1.06) and long duration of tenure (more than 49 months; SMR 2.22,  $p < 0.01$ ) (Mancuso 1980).

#### *Wagoner et al. (1980)*

Similarly, in an extended study performed by NIOSH (3055 workers, 47 lung cancer deaths) the highest rates of malignancies of the lung, trachea, bronchi were found among workers that were occupied less than five years and those the start of their tenure was more than 25 years ago (Wagoner et al. 1980). When lung cancer SMRs were calculated by latency the SMRs were 0.88 (9 deaths) for less than 15 years of latency, 1.16 (18 deaths) for 15-24 years' latency and 1.68 (20 deaths) for a latency of 25 years or more (95% confidence interval, CI being 1.0-2.6 for the latter SMR which means borderline significance at the  $p < 0.05$  level). However, within the latency categories there was again no pattern of increasing or decreasing SMRs by duration of employment (Wagoner et al 1980). Since the increases of mortality rates of lung cancer are not correlated with duration of tenure as a surrogate for exposure it has been assumed e.g. by IARC that high exposures may have been occurred among workers with short duration of employment, in particular during 1940s years including the years of World War II (IARC 1998). Potential confounding by a different distribution of smoking habits in the US population and in the beryllium cohort was considered and was calculated to potentially increase the lung cancer rate among the beryllium-exposed workers by 14%. On the other hand, when using the lower age-adjusted mortality rate for lung cancer among white males in the county (31.8/100 000) instead of the respective mortality rate in the US population (white males) as a whole (30.0/100 000) the lung cancer risk of the workers was underestimated by 19% (Wagoner et al. 1980).

#### *Conclusion*

Taken together, these early cohort studies are limited due to their lack of data on confounders such as smoker status and appropriately defined employment and exposure conditions. Thus, an association between exposure to beryllium and lung cancer mortality could not unequivocally be demonstrated.

## ***Studies using data of the Beryllium Case Registry***

### *Infante et al. (1980)*

The Beryllium Case Registry (BCR) was established in 1952 to collect data on the epidemiology, diagnosis, clinical features course and complications of beryllium-related diseases. Infante et al. (1980) investigated the lung cancer mortality among 421 workers who while alive entered the Registry with a diagnosis of chronic beryllium disease (CBD) or acute pneumonitis (acute beryllium disease, ABD). From 7 lung cancer deaths observed (3.3 expected based on national mortality rates; SMR 2.12; not significant) 6 cases occurred among workers who had a diagnosis of acute pneumonitis (ABD). Only one lung cancer death was observed among the workers with a diagnosis of CBD. Although the SMR for workers with a diagnosis of acute pneumonitis (ABD) was enhanced by nearly 3-fold there was no unequivocal evidence due to the above mentioned uncertainties about the national mortality rates during the years 1968-1975. Further limiting factors of this study were the small numbers of cases and the short follow-up- time of workers who entered the Registry after 1965 ( $\leq 10$  years). Important to this reference is a letter to the CDC, from Dr. Bayliss, objecting to having his name listed as a coauthor. He stated: "As I view it, there is one reason and one reason only why Drs. Wagoner and Infante, over the protests of me and others including the CDC review panel, refused to use the proper death rates; they want to be able to describe the study as demonstrating a statistically significant excess of respiratory cancer in beryllium workers – which is indeed precisely how the study is described in the abstract. The manipulation of the input data to permit assertion of a pre-ordained conclusion is not, in my view, evidence of intellectual or scientific honesty."

### *Steenland and Ward (1991)*

An extended study was conducted on the mortality rates of 689 persons who had entered the Registry up to 1980 (Steenland and Ward 1991). Mortality follow-up was extended to 1988. For comparison the US death rates were available for all years. There were not only an excess mortality of all cancers (SMR 1.51; CI 1.17-1.91; 70 observed deaths), an excess of lung cancer but also excess deaths from non-malignant respiratory diseases (SMR 34.2; 95% CI 29.1-40.0; 158 observed deaths) and all causes of deaths (SMR 2.19; 95% CI 1.17-1.91; 428 observed deaths). The SMR for lung cancer mortality was greater among cohort members with acute pneumonitis (ABD) than among those with CBD. Smoking was reported to be an unlikely confounder of the observed excess lung cancer since the study cohort smoked less (26% current smokers) than the US referent population (32%). Since the lung cancer SMR in this study population was higher than was found in other cohort studies, particularly among the study population with acute pneumonitis (ABD), it could be assumed that the Registry population had a higher exposure to beryllium.

## ***More Recent Studies Using Improved Assessments of Confounding, Type of Employment and Exposure***

### *Ward et al. (1992)*

A retrospective mortality cohort study of 9225 workers that were employed at seven beryllium-processing plants was conducted by Ward et al. (1992). In the total cohort, there were 3240 deaths (35%) and 269235 person-years of follow-up, of which 52% were person-years at risk 15 years or more after first employment in the beryllium industry. SMRs were calculated on the basis of US population as well as local county

mortality rates. The overall SMR for deaths of non-malignant respiratory disease was 1.48 (95% CI, 1.21-1.80), that for lung cancer was 1.26 (95% CI, 1.12-1.42; 280 observed deaths, based on US rates). At four of the six locations (the records of two plants were combined), the SMRs for lung cancer were greater than 1.00 but not significant, excess lung cancer rates were calculated for the two aforementioned plants in Lorain and Reading. The authors noted that cohorts in which there were elevated SMRs for pneumoconiosis or other respiratory diseases, presumably indicating higher exposure to beryllium also consistently had elevated SMRs for lung cancer. This correlation between non-malignant respiratory diseases and lung cancer led the authors to suggest without analysis or supporting data that the observed lung cancers were associated with high exposures to beryllium.

Lung cancer SMRs were stratified by latency at each plant and decade of hire. Although only three of the six locations showed higher SMRs for the 15-30 year and the >30 year category of latency, lung cancer SMRs increased stepwise for the total cohort with increasing latency. Lung cancer SMRs were significantly enhanced in three of four locations where workers were hired before 1950 (the period when exposures were also greater than subsequently). SMRs were also greater in four of the five locations where workers were hired between 1950-1959. In the total cohort, decade of hire was one of the strongest correlates of lung cancer mortality risk. Duration of employment had no effect. However, this surrogate for exposure is of minor relevance given the much higher exposures to beryllium prior to 1950 and the fact that 73% of the total cohort worked for less than five years in the beryllium industry.

Lung cancer SMRs based on US population and those based on local county mortality rates differed only slightly. The largest difference was found in the Reading cohort, Pennsylvania in which the SMR based on US rates was 1.24 and that based on the local county rate was 1.42. For all six locations, the lung cancer SMR based on US rates was 1.26 (95% CI, 1.12-1.42), whereas that based on local county rates was 1.32 (95% CI, 1.19-1.46). When lung cancer SMRs were adjusted for the effect of smoking habits at four of the plants in which a smoking survey was conducted in 1968 (covering 1466 (15.9%) of the 9225 persons of the cohort) the SMR for the total cohort changed from 1.26 to 1.12 and the SMRs in the two largest, oldest plants from 1.69 to 1.49 (Lorain, OH) and from 1.24 to 1.09 (Reading, PA). In addition, it is unclear if the assumption holds that smoking habits in the 1940s and 1950s when the exposures to beryllium were the highest were similar to those at the end of the 1960s years when the smoking survey was conducted. The authors estimated the contribution of smoking to lung cancer in the total cohort to be 13%, i.e., a SMR of 1.13 attributed to smoking compared to an SMR of 1.26 found in the total cohort.

*Sanderson et al. (2001a) and (2001b)*

A major limitation of the foregoing studies is the scarce knowledge of the exposure a) related to the time periods in the 1940s, 1950s and 1960s years and b) to the type of the jobs. The data from the two cohort studies using the BCR and from the study of Ward et al. (1992) suggest that workers were exposed to particular high beryllium concentration in their workplaces in the 1940s and 1950s years when there were few measures to reduce exposures. To improve the assessment of the workers' exposure to beryllium a job-exposure matrix for workers at the Reading plant was performed by the NIOSH group based on historical records on the duration of jobs and assessments on the basis of measurements in the air of workplaces (Sanderson et al. (2001a)). Since most of the measurements in the air of workplaces were carried out after 1970 and only few exist

from the time period before it is difficult to extrapolate to exposures during time periods of the 1940s and 1950s years when the exposures were probably the highest because of lacking ventilation and other measures for decreasing exposures at work places. It is known that first measurements at workplaces were initiated in 1947 after first reports had been published that beryllium may cause ABD and CBD and that further improvements of exposures to beryllium started about 1960 when a TWA of  $2 \mu\text{g}/\text{m}^3$  was introduced in some of the workplaces at the plant. Hence, it could be assessed that exposures in the 1940s and 1950s were considerably higher, probably by magnitudes, than in later decades when measures were gradually introduced. Also, between about 1960, 1970 and after about 1980 the beryllium exposures were gradually lowered by magnitudes. Despite these difficulties, the authors constructed a job-exposure matrix for more than 300 different selected jobs and different time periods. Nearly 200 measurements that had been carried out between 1947 and 1970 and nearly 7300 in the time period between 1971 and 1992 formed the basis for the job-exposure matrix. One of the main problems was the use of different sampling and analytical methods the results of which widely differed and were difficult to compare.

In a companion paper, a nested case-control study was conducted using the data of the previous cohort study of Ward et al. (1992) including a follow-up from 1988 until 1992 (Sanderson et al. 2001b), 142 lung cancer cases and 710 matched controls were identified within the cohort of 3569 male workers. Work history records including tenures were linked to quantitative, calendar-time-specific exposure estimates for each job to generate cumulative, average and maximum beryllium exposure metrics for each worker. Exposure metrics were generated by use of the job-exposure matrix (Sanderson et al., 2001a). Furthermore, tenures and exposure metrics were lagged 10 and 20 years to discount exposures that may not have contributed to causing lung cancer because lung cancer had already been induced, e.g. by earlier high exposures during short-term employments. By this method, analyses are restricted essentially to exposures that occurred early in calendar time, in the 1940s and 1950s. During this time period high exposures occurred and there were many short-term employees. Confounding by smoking was also evaluated. The majority of cases and controls were first hired during the 1940s with about 60% hired during 1941-1945. The average tenure was 3.7 years (median 5 months) for the cases and 5.5 years (median 11 months) for the controls. Almost two-thirds of the cases and over half of the controls were employed at the plant for less than 1 year. Comparison of the unlagged exposure metrics for cases and controls revealed that cases had significantly lower tenures and nearly significantly lower cumulative exposures. However, when beryllium duration of exposure and cumulative exposure metrics were lagged 10 and 20 years, the geometric mean tenures and cumulative exposure metrics were higher than those of the controls. The geometric mean average and maximum exposures were greater than for the controls and the difference was highly significant when the exposure estimates were lagged 10 and 20 years.

Analyses by quartiles of the tenure, cumulative, average and maximum beryllium exposure metrics lagging 0, 10 and 20 years showed significant increases of odds ratios ( $p < 0.05$  or  $< 0.01$ ) when lagging of 10 and 20 years was considered but the increases were not monotonic. The highest increases were found in the second and third quartiles. Using conditional logistic regression analysis of logs of continuous exposure variables strong positive associations were found with the log of the average or maximum exposure estimates lagged 10 and 20 years.

It is important to note that when lags were not taken, very few associations were found. The average and maximum categories of the cases and controls (including lagging of 10 and 20 years) were also compared by the exposure categories  $< 2 \mu\text{g}/\text{m}^3$ ,  $2\text{-}20 \mu\text{g}/\text{m}^3$ , and  $> 20 \mu\text{g}/\text{m}^3$ . The odds ratios across these categories consistently increased with increasing exposure although not in a monotonic manner. Odds ratios for unlagged exposures increased up to 2.2-fold (not significant) whereas lagged exposures significantly increased by about 2.1- to 4.6-fold ( $p < 0.05$  or  $< 0.01$ ). The confounders smoking and other chemicals at the workplaces than beryllium were better controlled than in previous studies.

*Levy et al. (2002)*

Levy et al. (2002) performed a reanalysis of the Ward et al. (1992) study by use of the same cohort. The following changes of the outcome were achieved when different methods were applied compared to the study of Ward et al.:

SMRs for lung cancer rates were based on estimated lung cancer rates for industrialized cities instead of lung cancer rates for the US population or counties since the two largest plants of the study, Lorain and Reading, are located in highly industrialized areas and the majority of the workers that were employed in these plants resided in or adjacently to these two cities. As a result, when based on the rates for industrialized cities the SMR for Lorain dropped from 1.69 based on US rates (SMR 1.60 based on the county rate) to 1.14 (95% CI, 0.86-1.48). Similarly, the SMR for Reading dropped from 1.24 based on U.S. rates (SMR 1.42 based on the county rate) to 1.07 (95% CI, 0.89-1.28). Both calculations indicate no significant differences in lung cancer mortality between the study populations of these two plants and the lung cancer mortality in the respective highly industrialized cities

*Levy et al. (2007)*

Levy et al. analyzed the same population as the nested control study of Sanderson et al. (2001b) but revealed a different outcome of the odds ratios when comparing non-transformed versus log-transformed exposure metrics in particular in combination with lagging of 10 or 20 years. As a consequence, the odds ratios using non-transformed metrics were not significantly enhanced thus challenging the conclusion of the Sanderson et al. study of providing further evidence that beryllium is a human carcinogen. Levy et al. suggest that the main reason for these differences may be a bias hitherto undetected and not yet discussed in the literature that may occur by the matching procedure of cases and controls if there is a major difference in the average age of cases and controls in combination with lagging. In the case-control study, the controls were, on average, 9.7 years older than the cases (age at death or last observation when alive). The control of the imbalance is important since age itself is a major confounder of lung cancer but the imbalance found is normally directed against enhanced odds ratios if controls are older than cases. When combining the matching procedure with lagging, the situation may become more complex since also other possible confounders such as year of birth, age at hire or age at termination of employment may be imbalanced in a complex way.

*Deubner et al (2007)*

This study demonstrated that the Deubner et al. 2007, reported on an empirical evaluation of a complex study design that has been used repeatedly with subtle variations. The study found that empirical evaluation helped to understand the behavior



of the study design and to investigate reasons for the study design behavior that were not initially discernible when considered from a theory point of view. Using the Sanderson study, the researchers applied the design study to a closely related cohort using randomly selected probands as cases. Values for average exposures were assigned to probands equal to, greater than, and less than those assigned to controls (matches). Under certain lag scenarios the nested study design produced a finding of higher average exposure in probands compared to their matches even when this was clearly not the case. The Sanderson study design produced a biased case-control lagged exposure difference under the null hypothesis and could not distinguish qualitatively between null and alternate hypotheses. Originally interpreted as clearly establishing a beryllium exposure - lung cancer response relationship the study demonstrated that this relationship was an artifact of methods and correction of methods leads to conclusion that the slightly (and questionably) elevated SMR in this large, heavily exposed and long follow-up US beryllium worker cohort is not beryllium exposure related.

Williams, 1996

This study is an analysis of 30 people (majority were fluorescent lamp workers or machinists: died from respiratory failure) from the UK Beryllium registry (total of 69 proven cases). Autopsy data on 19 of the subjects was generated or previously published. The survival times, from onset of disease to time of death, ranged from 2-29 years. No relationship was found between length of exposure and survival time, although the individual with the longest survival time was a machinist with significant exposure. Lung cancer was not identified in any of the cases. A common observation in all workers was interstitial pulmonary fibrosis with varying degrees of cystic change and pulmonary granulomas. Fibrosis was primarily observed in the upper zones. Larger nodules was observed in some individuals and consisted of hyalinised fibrous tissue with granulomas and Schaumann bodies. Isolated Schaumann bodies were found in the majority of the cases. Extrathoracic granulomas were rare but identified in a few individuals (although limited data existed) and only observed in liver and lymph node. Although no data is presented, it is stated that atomic absorption spectrometry was performed on tissue from some individuals and demonstrated beryllium in 12/13 cases tested.

Schubauer-Berigan, 2008

The authors of this publication re-analysed the dataset by Sanderson et al., (2001b) but evaluated different potential confounding effects: adjustments for birth cohort or age at hire was specifically investigated. An increased risk of lung cancer was associated with cumulative exposure (20 year lag) and average exposure. This risk was higher in workers born before 1900 than 1900 or later. However, when adjustment for birth cohort or age at hire was included, cumulative exposure was not associated with risk but average exposure was associated with risk when a 10 year lag period was included.

Levy, 2009

The cohorts originally analyzed by Ward et al (1992) were re-analyzed in this study by using a Cox proportional hazards model. The focus of the study was primarily to look at the endpoints in the Ward et al study where an increased risk of lung cancer was found: earlier plants, increased latency, and decade of hire. Six covariates were included in the current analysis: date of birth, person-years of follow up, cohorts, employment tenure, date of hire, and age of hire. Smoking or other known risks of lung cancer was not included as confounding effects in this study. There was no increase in lung cancer in workers hired in the 1940s relative to workers in the 1950s. There was an increase in

lung cancer risk in workers hired in the 1950s relative to the 1960s; however it is speculated that the increased risk may reflect lower rates of smoking in the 1960s. An increase in lung cancers from workers at earlier plants was not found. Finally, when the covariates were taken into consideration, there was no effect of latency period on lung cancer risk.

Deubner, 2009

No new analysis is presented in this publication. It is a comment by Deubner on the current understanding of the relationship between beryllium exposure and lung cancer taken into consideration the comments by other epidemiologists. It is concluded that the Levy et al 2007 study is an improvement of the study by Sanderson et al, 2001. Finally, the Schubauer-Berrigan et al, 2008 study is considered the currently best analysis as it includes an additional confounder source. However, the author argues in this comment that more analysis needs to be done in order to determine the relationship between occupational exposure to beryllium and risk for lung cancer. The current knowledge indicates that employment duration or cumulative exposure to beryllium is not positively associated with lung cancer.

APPENDIX 5

**Beryllium SMR Summary From Epidemiology Studies**

*Table 1 NIOSH 2001 Beryllium Worker Lung Cancer SMR by Plant*

Facility	SMR	p	LC Cases	Population
<b>Lorain</b>	<b>1.69</b>	<b>&lt;0.01</b>	<b>57</b>	<b>1,192</b>
<b>Reading</b>	<b>1.24</b>	<b>&lt;0.05</b>	<b>120</b>	<b>3,569</b>
Lucky	0.82	>0.05	9	405
Cleveland	1.08	>0.05	44	1,593
Elmore	0.99	>0.05	15	1,323
Hazleton	1.39	>0.05	13	590
Multiple	1.67	>0.05	13	257
Unknown	1.33	>0.05	9	296
<b>Total</b>	<b>1.26</b>	<b>&lt; 0.01</b>	<b>280</b>	<b>9,225</b>

*Table 2 Beryllium Workers SMR for Lung Cancer by Decade of Hire*

Decade	SMR	p	LC cases
<b>1940s</b>	<b>1.42</b>	<b>&lt; 0.01</b>	<b>177</b>
1950s	1.24	> 0.05	85
1960s	0.62	> 0.05	18
Total	1.26	<b>&lt; 0.01</b>	<b>280</b>

*Table 3 Beryllium Workers SMR for Lung Cancer by Years Worked*

Years	SMR	p	LC Cases
<b>&lt; 1</b>	<b>1.32 s</b>	<b>&lt; 0.01</b>	<b>152</b>
1-5	1.19 ns	> 0.05	61
5-10	1.26 ns	> 0.05	21
>10	1.19 ns	> 0.05	46
<b>Total</b>	<b>1.26 s</b>	<b>&lt; 0.01</b>	<b>280</b>

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