Regulatory Toxicology and Pharmacology 53 (2009) 174–185

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

# Reconstruction of historical exposures in the US nickel alloy industry and the implications for carcinogenic hazard and risk assessments

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ARTICLE INFO

*Article history:*
Received 2 July 2008
Available online 23 January 2009

*Keywords:*
Nickel alloy industry
Reconstructed historical exposures
Monitoring
Occupational exposure limits
Hazard identification
Risk assessment

ABSTRACT

Recently, various regulatory authorities have been reexamining the potential carcinogenic hazards and risks associated with exposures to nickel and certain nickel compounds. In making their assessments, the authorities have focused on occupational cohorts at facilities where nickel-containing sulfidic ores were processed and where increased lung and nasal cancer risks were found in specific groups of workers. Little attention, however, has been paid to the vast number of workers in nickel-using industries, where no excess respiratory cancer risks have been observed. In this paper, the historical exposures of one such group of workers engaged in the production of nickel alloys are reconstructed, and the implications for cancer risk assessments are analyzed. The results indicate that nickel alloy workers were exposed to insoluble oxidic and metallic nickel species at levels comparable to those found in certain nickel processing cohorts; yet they experienced no increase in respiratory cancer risks. This suggests that extrapolating risks from certain primary nickel producers to other nickel industry sectors may not be appropriate.



## 1. Introduction

Recently, various regulatory authorities have been reexamining the carcinogenic hazards and risks associated with occupational exposures to nickel and certain nickel compounds (Cal OSHA, 2005; EURA, 2005a,b). It also appears that worker/public health evaluation agencies—most notably, the International Agency for Research on Cancer—will be reexamining the carcinogenic hazards of metals and other substances (including nickel compounds) in the near future (IARC, 2008). Studies of primary nickel workers involved in the processing of nickel from sulfidic ores (the so-called "high risk" cohorts) undoubtedly will be the focus of any future deliberations of these bodies, as these are the studies where occupationally-related excess respiratory cancer risks in nickel workers have been observed (Roberts et al., 1989; ICNCM, 1990; Easton et al., 1992; Andersen et al., 1996; Grimsrud et al., 2002, 2003).

By contrast, scant attention has been paid to the respiratory carcinogenic risks, if any, associated with inhalation exposures to nickel in other industry sectors, despite the fact that these sectors employ the vast majority of nickel industry workers. Studies of workers involved in the smelting and refining of lateritic ores (which do not contain nickel sulfide minerals) and studies of workers in nickel-using industries—including plating, nickel alloy and stainless steel production, stainless steel fabrication, certain welding operations, and barrier manufacturing in the enrichment of uranium—have consistently shown no occupationally-related respiratory cancer risks (Sivulka et al., 2007).

It would appear, therefore, that the human evidence for nickel-related carcinogenicity is confined to nickel-producing industries involved in the processing of sulfide-containing ores. That being the case, it may not be appropriate to apply the results of carcinogenic risk assessments based on exposure and mortality data from the high risk nickel cohorts to other nickel workers, particularly as the latter (1) would not have been exposed to the same mix of nickel species and other carcinogenic agents as the workers in the high risk cohorts and (2) have shown no evidence of occupationally-related elevated respiratory cancer risks.

In order to test this theory, a suitable cohort would have to be found in the nickel-using industry that would be comparable to the high risk cohorts with respect to size, concentrations of nickel species, and follow-up. The closest such group is the cohort of more than 31,000 US nickel alloy workers studied by researchers at the University of Pittsburgh (Redmond et al., 1996; Arena et al., 1998). Roughly 86% of these workers were first employed between 1905 and 1959, with the greatest influx of hires (80%) occurring during World War II and the 10 years following the war. Age at first hire was ⩾25 years for the majority (65%) of the cohort. Approximately 87% of the cohort had a minimum of 28 years of follow-up, and 70% had at least 33 years of follow-up. Given that occupationally-related lung cancers in the high risk nickel refinery

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doi:10.1016/j.yrtph.2009.01.006

cohorts have been shown to occur as early as 10 years since first employment (Doll, 1984), with latency peaking at 15–30 years (Grimsrud et al., 2003), the Arena et al. study should have substantial power to detect excess nickel-induced lung cancer risks at comparable levels of nickel exposure. The statistical power of the study to detect a small relative risk of 1.1 was more than 90%. The cohort showed no evidence of increased lung cancer risks in comparison to local populations, and any modest excess lung cancer risks that were observed in the workforce when compared to the general US population were not attributed to employment in the nickel alloy industry, but rather to cigarette smoking or demographics based on geographic location.

The remaining question is whether nickel exposure levels in this US nickel alloy cohort were comparable to nickel exposure levels in the high risk cohorts where nickel was refined from sulfidic ore. The Arena et al. (1998) study itself does not answer this question because the average exposures reported in the study were relatively low and likely understated. The reason for this is that the reported exposure measurements were obtained in the late-1970s, whereas the actual exposures most relevant to respiratory cancer mortality experienced by cohort members occurred in prior decades. In addition, almost all of the exposure data reported in the study came from a single plant, which may or may not have been adequately representative of the other plants in the study or the industry as a whole. Thus, a reconstruction of historical exposures—not only with respect to this cohort, but also with respect to the overall specialty steel and nickel alloy industry within the US—is undertaken here, so that the implications of the epidemiological findings of the Arena et al. study can be better evaluated in comparison to what has been reported for nickel production workers in industries where nickel was processed from sulfidic ores.

## 2. Background

In the early 1980s, Redmond and coworkers undertook a historical prospective study of workers employed in the production and fabrication of specialty steels containing nickel (Redmond, 1984). The cohort consisted of approximately 28,000 workers employed in jobs in 11 major work areas at 12 plants. Work histories and vital status were followed through 1977. Mortality patterns were analyzed by work areas and length of employment. Cohort mortality when compared to the general US population showed no overall statistically significant increased risk for respiratory cancers (including two nasal cancers; SMR = 115.8; $p = 0.52$), but a modest excess risk of lung cancer was seen in white male workers employed in allocated services. Redmond noted that the latter observations were consistent with a number of underlying hypotheses (both occupational and non-occupational), but reached no firm conclusions with respect to the etiology of the cancers. Further follow-up of the cohort was recommended.

In a follow-up study that was conducted on these workers (Arena et al., 1998), a thirteenth plant was added to the study, resulting in a cohort of more than 31,000 workers. The vital status of the workers was followed an additional 10 years, but work histories were not updated. Since previous studies of other nickel workers (e.g., primary nickel workers in Wales; Peto et al., 1984) had shown that comparisons to local populations are an effective way to control for variations in background risk, Arena et al. were interested in comparing the alloy cohort's mortality to both the general US population and sub-populations surrounding the plants. The authors felt that the overall cohort was well suited for comparisons to local populations as the alloy workers were employed in plants surrounded by large Standard Metropolitan Statistical Areas (often in excess of 1 million people), of which the nickel worker cohorts comprised only about 0.2%.

Results of the study showed a modest statistically significant excess risk of lung cancer in white male workers (mainly employed in allocated services) when compared to the general US population. However, there was no evidence of a dose–response relationship based on number of years of employment for any of the work areas (including allocated services) or gender/race groups studied. When comparisons were made with local populations, there was no significant excess of mortality for lung cancer within the overall cohort or for any gender/race and/or specific work subgroups, including allocated service workers. Likewise, there was no evidence of a dose–response relationship for any of these groups. No additional nasal cancers were observed despite the increase in follow-up. In totality, the findings suggested that the modest excess lung cancer risks observed in comparison to the general US population were not occupationally-related, but rather due to other factors such as cigarette smoking or demographics. This is supported by a lack of evidence of excess lung and nasal cancer risks in other nickel alloy workers who have had no employment in, or possible exposures due to, the processing of nickel-containing sulfidic ores (Cox et al., 1981; Enterline and Marsh, 1982; Moulin et al., 1990, 2000; Hansen et al., 1996; Jakobsson et al., 1997; Sorahan, 2004).[1]

Mortality in these two studies was analyzed by duration of employment and length of time since first employment. Although exposure data were reported in the study, they were used mainly as an indicator of relative nickel exposures in different work areas. This was due to the fact that the exposure data obtained were confined to the late-1970s and, thus, did not necessarily correlate to the employment history of the overall cohort. Taking into consideration factors such as time since first employment (80% hired before 1956) and the latency of nickel-induced lung cancers (15–30 years), it can be surmised that the exposure period of greatest relevance to the lung cancers seen in this study would have been sometime between the early-1940s to the mid-1970s. Due to improvements in engineering and environmental controls over time, there is no question that exposures in the earlier years would have been higher than those reported in the study. The magnitude of these exposures and the implications of this for hazard and risk assessments of these workers is the focus of the remainder of this paper.

## 3. Approach to historical exposure reconstruction

### 3.1. Data collection

Of the 13 plants included in the 1998 follow-up study by Arena et al., four have since closed operations. Of the eight companies currently operating the remaining plants, five agreed to participate in the current study. These companies provided measurements pertaining to the plants that were in the original study, as well as for additional plants similar in processes and operation, resulting in a fairly robust and comprehensive data base. In addition, historical narratives on the operations of nine of the original plants were collected either through the participating companies or through archived materials. Additional sources of information on the original plants included data available in published papers

[1] It should be noted that two other ''possible'' nasal cancers were observed in ''non-refinery'' alloy workers at a plant in Huntington, West Virginia (Enterline and Marsh, 1982). These cancers were originally coded as bone cancers, but could have had an origin from the nasopharynx. However, as noted by Doll (1984), while ''suggestive,'' these nasal cancers "should not weigh heavily" as the two men presenting with these cancers could readily have had exposure to nickel subsulfide dust from calcining operations at the plant, even though they were not believed to have worked directly in the calciners. Regardless, they were noted to have been exposed to high-temperature nickel–copper oxides in acid reclaim, which would have been unique to this plant. For the implications of this, see Section 5.

and data provided in reports submitted to regulatory bodies. Finally, the expert advice of industrial hygienists and metallurgists within the companies was sought to answer questions pertaining to the operation of the plants, such as feed materials used, changes in ventilation over time, and types of alloys produced.

Thus every effort was made to gather all available modern-day and historical exposure measurements for these plants and to evaluate those data in light of narrative materials and historical knowledge of the plants to confirm that the quantitative measurements obtained were in agreement with what was qualitatively known about these plants.

### 3.2. Classification of work area measurements

In the original study, each job in a worker's history was coded according to specific job titles and departments. These were standardized across all plants and assigned to 11 major work areas common to all of the participating plants. The companies participating in this study were provided the work area descriptions from the original Redmond study (Redmond et al., 1983; unpublished report) and examples of types of jobs that might be found in these work areas (Caplan et al., 1979; unpublished report) and asked to use their best judgment in coding their measurements according to these descriptions. Brief descriptions of nine of these work areas follow.

#### 3.2.1. Production processes

*Coldworking: involves* changing the size and shape of the alloyed material below its recrystallization temperature. Most cold working takes place at ambient temperatures, although some heating occurs due to friction in the forming process. Examples of cold working include: cold rolling, wire drawing, plate leveling, coining, stamping, and spinning.

*Hot working: involves* changing the size and shape of the alloyed material above its recrystallization temperature. Types of hot working include: hot rolling, forging, extrusion, billet heating, and plate leveling.

*Melting: involves* melting of alloys in a variety of furnaces. Types of melting work include: ladle pouring, ingot pouring, mold stripping, furnace charge preparation, investment casting pouring, and mold breaking.

*Grinding: involves* the removal of a metal(s) by using an abrasive material in the form of a bonded wheel or belt; may occur in cold working, hot working, and/or foundry operations and can be done either wet or dry. In the former case, water containing soluble oil is used as a coolant in the grinding process. Types of grinding include: spot, surface, swing frame, belt, pedestal and bench grinding.

*Foundry: involves* the melting and casting of alloys into shapes using various molds.

*Pickling and cleaning: involves* the use of various acids and alkaline materials to remove metal oxides, greases, and dirt from the product. Pickling and cleaning are often carried out as part of cold working operations. Many pickling and cleaning baths are used at elevated temperatures; exposures to metals are generally low.

#### 3.2.2. Non-production processes

*Administrative and technical: involves* activities such as research, engineering, quality control, office, and custodial.

*Allocated Services: involves* four divisions: pattern and die, guards and janitors, maintenance and support services. Maintenance activities include: welding and fabrication; machining; pipefitting; mechanical work; repair of large assemblies; and maintenance of service systems. Guards provide security services at entrance points of the facilities and perform patrol duties. Janitors engage in cleaning activities (both mill and administrative). Pattern and die workers design and machine shapes that are used for molds in casting. Support Services is a "catch all" reserved for other undesignated jobs. In the original unpublished report (Redmond et al., 1983), most of the exposures of those working in allocated services were noted to be unrelated to production processes and, thus, included exposures to welding fumes, dusts, solvents, asbestos, lubricants, cleaning materials, resins, and other chemicals. But inhalation of nickel-containing substances could have occurred, depending on the nature of the job being performed.

In addition to these work areas, three other areas constituted part of the original alloy study: "other workers," "powder working," and "X-rays." No description of "other workers" is available; thus, this work descriptor has been excluded from the current study. Powder workers are involved in the handling of high-purity metal powders. However, "powder working" is excluded, herein, as only one plant was actually involved in powder metallurgical operations and the total number of workers employed was very small (only 216). "X-ray" workers comprise technicians whose job is to inspect metal parts for defects. In actuality, such workers rarely use radiology; inspection is usually done through other means such as the use of ultrasound or magna-flux testing. As they, too, constituted a small percentage of the overall cohort (only several hundred workers) and had practically no exposures to metal dusts, they have also been excluded from this study.

Most of the data were measurements taken on individual workers identified by job title. No effort was made to standardize the various job titles across companies. As noted above, companies were simply asked to use their best judgment in coding their measurements according to the work area descriptions provided in the unpublished report of the original Redmond study. This undoubtedly led to some variations by company in the recording of measurements by work area. While this variation is unquantifiable, it is likely to be minimal, as companies were provided example lists of the types of jobs that might be found in these specific work areas (Caplan et al., 1979).

### 3.3. Personal and stationary sampler air monitoring measurements

Both personal and stationary air monitoring measurements were obtained from company records. Little is known about the types of stationary samplers that were used. Where companies did provide such information, samplers were noted to be high-volume samplers. Stationary samples comprised only 4% of the total measurements obtained in this study.

In contrast, 96% of the measurements were taken in the breathing zone of workers. The founding in the early-1970s of the National Institute for Occupational Safety and Health (NIOSH)—with its attendant requirements for companies to comply with specific methods for monitoring workers—assured that companies monitored their workers similarly. Specific methods for sampling the breathing zone of workers generally consisted of using a 2- or 3-piece filter cassette containing a 37-mm diameter cellulose mixed-ester membrane filter with a 0.8-μm pore size. Use of a battery-operated vacuum pump was required; the pump had to be capable of operating at 2.0 l/min for up to 8 h (NIOSH, 1974). NIOSH established specific procedures for calibrating the pump, sampling workers, and analyzing the mass of nickel on the filter. While some of these methods have been revised over time, the essential procedures have remained the same. Thus, most measurements compiled in the 1970s through the present are believed to have been obtained through compatible measurement techniques.

With very few exceptions, measurements taken prior to 1970 were also based on personal samples, but they were obtained from midget impingers reported to be placed in the breathing zone of workers. As sampling instruments, impingers have limitations in that they only provide a count of particles, usually expressed in terms of millions of particles per cubic foot or MPPCF; they do not, however, measure the overall mass of particulate matter. Thus, to use these measurements it is necessary to first convert the particle counts into mg particulate/$m^3$ and then apply an estimate of the percentage of nickel to the particulate concentration (Vincent, 2007).

A total of 423 individual impinger measurements were taken in 1937, 1940, and every year between 1954 through 1963. They were mainly from two working areas (six different melting departments, five different grinding departments) within two companies that participated in the Redmond/Arena study. Although most of the impinger data were available only as averages, a few individual measurements were provided, including a few measurements from cold working operations.

The bulk of the impinger measurements in the present study came from a plant that closed in the mid-1970s, which ruled out the ability to conduct a field study in which conversion factors could be empirically derived by comparing simultaneous measurements with a midget impinger to those taken with a 37-mm cassette sampler. However, such a study was conducted—at least for melting operations—in the 1970s in the other plant (Warner, 1976). In this study, a factor of 5.2 was derived to convert particle counts (expressed as MPPCF) to mg particulate/$m^3$ in melting operations. Descriptions of melting operations in the two plants suggested that it would be reasonable to apply this factor to the impinger data for melting in both plants. An additional factor of 0.07 was applied to account for the average percentage of nickel (7%) found in total aerosol particulates within melting operations across the original nine plants for which such data existed. This resulted in a total conversion factor of 0.36 ($5.2 \times 0.07 = 0.36$) for melting operations.

In the case of grinding operations, conversion factors from a study by Bloomfield and DallaValle (1935) were applied to the grinding data. Although this study is an early one, it, too, found an empirical correlation between particle counts and gravimetric concentrations by weighing 600+ impinger samples on which counts had been made. These samples had been taken from various industry sectors, including those involved in polishing and grinding. A factor of 1.9 was derived to convert particle counts (expressed as MPPCF) into gravimetric concentrations in grinding and polishing operations. As the period in which this study was conducted was viewed as likely comparable exposure-wise to the periods (1940s–1960s) in which impinger measurements were taken in the above-mentioned alloy plants, the conversion factor of 1.9 was applied to the impinger data collected in grinding operations within the alloy plants. An additional factor of 0.2 was applied to account for the estimated average percentage of nickel (20%) found in total aerosol particulates within grinding operations across the original plants for which such data existed. This resulted in a total conversion factor for grinding of 0.38 ($1.9 \times 0.2 = 0.38$).

### 3.4. Speciation of nickel

Nickel speciation studies conducted in the nickel alloy industry have shown that approximately 85% of nickel exposures are composed of oxidic nickel and about 7% are metallic nickel (Vincent et al., 1995). Vincent and his colleagues sampled seven different departments within four production processes (*i.e.*, melting, grinding, hot working, and cold working) (Tsai et al., 1996). While the breakdown of insoluble nickel species per department was not provided, based upon the knowledge of the feed materials that are used in alloy production (*i.e.*, generally metallic nickel or nickel alloy scrap), it is highly unlikely that other insoluble nickel species would be present.[2] Moreover, it is quite possible that the amount of oxidic nickel reported by Vincent was underestimated, as recent analyses of the sequential leaching method used by Vincent to speciate his samples has shown that, occasionally, small particles of oxidic nickel (the residual nickel species in the procedure) may be leached out in earlier stages and misclassified as ''sulfidic'' or ''soluble'' nickel (Conard et al., 2008). This likely was the source of ''suflidic'' nickel reported by Vincent.

Vincent also found a small percentage of soluble nickel (≈3–4%). As noted above, some of this ''soluble'' nickel may well have been small particles of oxidic nickel. However, some may have come from pickling and cleaning operations. Although not specifically mentioned in Vincent's paper, it is possible that some pickling and cleaning workers were included in his analysis as these activities often occur in tandem to cold working. While workers in pickling and cleaning will be exposed to both soluble and insoluble nickel, exposures to soluble nickel will be low and largely confined to pickling operations. This is due to the widespread use (both past and present) of local exhaust ventilation over the surface of the acid baths within pickling operations so that the spread of uncontrolled corrosive aerosols to other areas of a plant can be avoided (Caplan et al., 1979). Thus, even in early years, some form of ventilation (e.g., large fans to draw the acidic fumes into tunnels under the cleaning tanks) was often used; in later years, acid scrubbers at strip lines were often installed. Due to this practice, soluble nickel has never been regarded as a significant component of workplace exposures within the nickel alloy industry.

### 3.5. Summarization of work area measurements

Both personal and stationary measurements obtained from company records were grouped by 10-year intervals, starting mainly in the 1950s (with a few measurements taken in the late-1930s to the early-1940s) and continuing to the present. In some instances, data obtained from early company reports and/or public documents consisted of summary statistics (ranges of values, numbers of samples, and average nickel levels) for groups of nickel workers in different departments. The number of samples upon which the means were computed was often known, but it was impossible to calculate standard deviations from such information. This was particularly true of data taken prior to the mid-1970s. In these cases, weighted means (based on numbers of samples) were computed for work areas. An index of the variability of these means (and to some extent, the underlying distribution of measurements) is provided by reporting the maximum mean value. In work areas and time periods where individual data were available, the estimated 95th percentile of the distribution of measurements is provided to give a better sense of the distribution of measurements (and variability of individual nickel exposures). For work areas with more than 100 measurements, the estimate is based on the observed 95th percentile of the empirical distribution of measurements, and for work areas with smaller numbers of measurements, it is based on the mean + 1.65 × the standard deviation of measurements.

In constructing the database for this effort, data values that were clearly aberrant relative to the rest of the data distribution were discovered (e.g., 3–4 orders of magnitude greater than mean values). Where the data were noted to be ''contaminated samples,'' such values were excluded. Where no explanatory comments were provided, it was desirable to exclude large values which would clearly distort summary statistics that were being used to characterize nickel exposures. At the same time, it was important that any screening technique that was devised not be so stringent that it would exclude large values that represented a substantial part of the probability distribution. The strategy adopted was to exclude data that were more than five standard deviations from the mean of the measurement distribution in

[2] It should be noted that Vincent did report a very small percentage of ''sulfidic'' nickel present, but this is likely a misclassification (see above), as alloy production does not lend itself to the presence of sulfides.

each work area. This was judged to strike an appropriate balance, screening out those measurements that were clearly aberrant, but keeping the exclusion rate at a reasonably low level (39/ 6986 ≈ 0.6% of measurements).

*3.6. Reconstruction of missing exposures*

Work areas with no available measurements for different periods of time were estimated by back-extrapolation using data-driven multipliers (Seixas and Checkoway, 1995). That is, for work areas where there were no data for specific time periods, exposures were estimated by extrapolating back from time periods where there were measurements, using the temporal trends in nickel concentrations for other work areas where data were available over time (in particular, melting and grinding areas with impinger data taken in the 1940s–1960s). These estimated exposures were then compared to historical descriptions of the plants to assure that the measurements derived were in agreement with descriptions of the working conditions within the plants. Such extrapolation methods have been applied to other nickel cohorts (Grimsrud et al., 2000). However, in the current study, the multipliers used had the added advantage of incorporating actual historical measurements as opposed to being derived solely from current exposure measurements and subjective judgment.

*3.7. Estimation of nickel exposure in nickel alloy workers*

The estimates of past exposures-based upon actual measurements and historical knowledge of the processes, as well as the pattern of employment in the high nickel alloy workers studied by Arena et al. (1998)—were used to obtain an average exposure estimate for the cohort. This, in turn, was used in conjunction with the observed respiratory cancer mortality to make a quantitative assessment of nickel-related risk.

To estimate the average work area exposures, the distribution of hires summarized in 5-year periods by Redmond et al. (1983, 1996) was utilized. In addition, the (unknown) average length of employment was assumed to be either 10 or 20 years. The larger of these two numbers is clearly an overestimate of the average length of employment, given that Arena et al. (1998) reported that only 15% of the person years in the cohort were distributed among workers with more than 20 years of employment. The average workplace exposure obtained under this assumption is an extreme lower bound because, in contrast to assuming a 10-year average length of employment, the assumption of a 20-year average length of employment places a higher percentage of the cohort's total exposures in the later years, when exposure levels were lower. The work area averages were then aggregated to obtain average exposure estimates for the cohort under the two-duration of employment assumptions. These overall cohort averages were calculated by weighting the work area averages by the mean number of workers who had been reported to have ever worked in these areas.

## 4. Results

A total of 6986 measurements from the 1940s to the present were collected (Table 1). These measurements came from 45 plants, all but three of which are owned by the five companies that agreed to participate in the current study. These 45 plants include nine of the 13 plants whose workers were studied by Arena et al. Most measurements were based on personal samples; this applied to every 10-year period examined. Roughly 24% of the measurements came from nine of the original plants studied by Arena et al.; measurements from these plants constituted ≈90% of the measurements most pertinent to reconstructing historical exposures (*i.e.*, those in the 1980s or earlier).

Table 2 shows the breakdown of exposures for different work areas across time. While research has shown that the 37-mm sampler used to collect the measurements in Table 2 progressively undersamples particles of increasing size with respect to the fraction of particles that are truly "inhaled" by the worker (Vincent, 2007), the measurements shown are reported as they were recorded, that is, as "total" nickel. Fig. 1a graphically depicts the mean values in Table 2 that are based on actual measurements collected in the alloy plants. The figure clearly indicates that airborne nickel exposures decreased considerably over time across all work areas, with the exception of allocated services and administrative and technical work areas in which measurements were taken only in the 1980s and later. These decreases are particularly evident in the observed pattern prior to the late-1970's.

As discussed above, the pre-1970 values for melting and grinding came from impinger data converted to gravimetric measurements using conversion factors empirically derived. In the case of melting, the average particle counts collected by the impingers ranged from 2.1 to 19.5 MPPCF. Using the conversion factor derived above (0.35), the weighted mean for all melting operations expressed in terms of "total" nickel was approximately 2.2 mg Ni/m$^3$. In the case of grinding, the average particle counts collected from the impingers ranged from 1.8 to 7.8 MPPCF. Applying the factor of 0.38 derived above, the weighted mean for all grinding operations expressed as "total" nickel was approximately 1.7 mg Ni/m$^3$.

Mean values for the empty, shaded cells in Table 2 were estimated by extrapolation using data-driven multipliers derived from the temporal patterns in mean nickel levels shown in Fig. 1a. Table 3 shows the multiplicative factors calculated from work areas where exposure measurements existed for different time periods. Mean exposure values for melting and grinding in the period encompassing the 1940s through the1960s were higher than those in the early-1970s by multiplicative factors of 12.3 and 2.4, respectively. The plausibility of the magnitude of these factors was supported by the narrative materials which described working conditions in production areas as being quite dusty. This was true not only for grinding and melting, but for hot working and cold working as well. This was supported by the particle counts for cold working, which while limited (only two measurements with an

**Table 1**
Profile of measurements taken within the US nickel alloy industry: number and type of measurements by 10-year time periods.[a]

| Time period/plants | 1940s Through 1960s | 1970s | 1980s | 1990s | 2000s | Total measurements |
|---|---|---|---|---|---|---|
| All plants | 7 (A)[b] | 127 (A) | 18 (A) | 40 (A) | 62 (A) | 254 (A) |
| | 416 (P)[c] | 429 (P) | 476 (P) | 3763 (P) | 1648 (P) | 6732 (P) |
| Plants 1–9 only | 7 (A)[b] | 127 (A) | 18 (A) | 2 (A) | 5 (A) | 159 (A) |
| | 416 (P)[c] | 429 (P) | 311 (P) | 173 (P) | 173 (P) | 1502 (P) |
| Total "*N*" all plants | 423 | 556 | 494 | 3803 | 1710 | 6986 |

[a] A, area samples; P, personal samples.
[b] Impinger measurements taken in the early-1940s. These were stationary samples.
[c] Midgit impinger samples placed in the breathing zone of workers taken in the 1950s through the 1960s.

**Table 2**
Comparisons of mean "total" nickel exposures (mg Ni/m$^3$) and their variability for various work areas by time.[a]

| Work area[b] | 1940s/1960s | Early-1970s | Late-1970s | 1980s | 1990s-Present |
|---|---|---|---|---|---|
| Melting | 2.22<br>9.76$^m$<br>(U)[c] | 0.18<br>2.70$^m$<br>(187) | 0.05<br>0.15<br>(53) | 0.04<br>0.15<br>(124) | 0.03<br>0.09<br>(679) |
| Grinding | 1.68<br>2.96$^m$<br>(U)[c] | 0.69<br>2.65$^m$<br>(59) | 0.12<br>0.41<br>(49) | 0.22<br>1.10<br>(197) | 0.05<br>0.20<br>(680) |
| Cold working | | 0.24<br>0.36$^m$<br>(82) | 0.06<br>0.15<br>(13) | 0.02<br>0.09<br>(58) | <0.01<br>0.03<br>(2229) |
| Hot working | | 0.52<br>1.02$^m$<br>(70) | 0.10<br>0.30<br>(23) | 0.07<br>0.22<br>(90) | <0.01<br>0.02<br>(576) |
| Pickling and cleaning | | | 0.02<br>0.08<br>(13) | 0.03<br>0.08<br>(5) | <0.01<br>0.01<br>(354) |
| Administrative and technical | | | | <0.01<br><br>(1) | 0.01<br>0.04<br>(95) |
| Allocated services | | | | 0.08<br>0.20<br>(11) | 0.01<br>0.04<br>(863) |

[a] The first entry in each cell is the overall mean value for the work area. The second entry is the 95th percentile of data distribution; when this entry is superscripted with an "m", it represents the maximum mean value (e.g., an annual mean) from the group of mean values that contributed to the overall work area mean. Values in parentheses are the numbers of measurements.

[b] While "Foundry" was originally included in the Arena et al. exposure table, only 14 measurements were noted to be for foundry work in the new data base, all from the 1990s to the present. Because of the uncertainty in extrapolating back from such a limited sample, the foundry work area was not included here. Measurements for jobs that might have been coded as foundry work in the Arena et al. study have probably been categorized as "melting" in the new data base.

[c] Four hundred and twenty one impinger measurements were taken in various melting and grinding operations during the 1930s through the 1960s. The total number of measurements across the two areas is known in each year, but the total number of measurements in each work area is unknown (U). Two impinger measurements were also taken in Cold Working; their average particle counts were 29 MPPFC. However, due to inadequate information in which to convert particle counts into gravimetric measurements, these data were not included in this and subsequent tables.

average count of 29 MPPFC), suggested operations that were as dusty as grinding and melting.

In the case of non-production areas, while the narrative materials shed limited light on the dustiness of these operations, it is logical to assume that if production process workers had dustier exposures in the earlier years, then non-production workers—particularly those in allocated services which included maintenance, janitors, guards, etc.—would also have had proportionally higher exposures during these years.

Thus, it was deemed appropriate to apply multiplication factors from areas that had exposure data in the early years to areas that lacked such data. But the choice of what factor to use remained uncertain, requiring further analyses. In the case of melting, the narrative materials suggested that temporal changes in nickel concentrations appeared to be due to technological changes (e.g., upgrades in the types of furnaces used), as well as changes in ventilation (e.g., installation of bag houses), which is why the multiplicative factor for melting is quite high (12.3). On the other hand, the temporal changes seen in grinding (much smaller than in melting; 2.4), appeared mainly due to improvements in housekeeping and local ventilation. Because it was unclear whether technological changes were being implemented in work areas other than melting (and if so, to what degree), the smaller of these two factors (2.4) was used to extrapolate nickel values prior to 1970 from measurements in the early-1970's for the remaining work areas where measurements were absent. By using the lower factor, changes in other work areas were assumed to be due mainly to improvements in environmental controls. This may or may not have been a correct assumption, but it constituted a conservative one.

In workplaces where measurements were absent in the early-1970s (*i.e.*, pickling and cleaning, administrative and technical, and allocated services), an additional multiplicative factor of 5.7 was used to extrapolate nickel values for the early-1970s. This factor was derived as the average of the multiplicative factors obtained by dividing the observed means in the early-1970s in melting, grinding, cold working, and hot working by the corresponding mean values in the late-1970s/1980s. In extrapolating to the early-1970s, measurement averages for both the 1970s/1980s and the late-1970s/present were considered as potential points of departure. The late-1970s/1980s period was chosen as the better departure point, as it was closer in time to the early-1970s, and there was evidence of decreasing exposures after 1990.

Fig. 1b shows the actual and extrapolated exposure data from the 1940s to the late-1970s, and Table 4 provides weighted averages within and across work areas, based on the hire years of the workforce studied by Arena et al. All of these workers were hired prior to 1970, with 70% hired before 1955. Under each of two assumptions concerning average length of employment (10 and 20 years), more than 90% of the employment/nickel exposure for the cohort occurred prior to 1975. As a result, weighted averages of the measurements across time, based on percentages of employment/exposure, indicate that the different assumptions concerning length of employment have only a small effect on the exposure estimates (7–15% for different work areas, 11% for the overall average).

As indicated in the section describing methods, the 20-year average length of employment assumption was included to provide an extreme lower bound on the estimated average exposures. Therefore, a value of 0.67 mg Ni/m$^3$, which is the midpoint of the estimates under the 10 and 20 year employment assumptions (0.70 and 0.63 mg Ni/m$^3$, respectively) is a reasonable estimate of the cohort-wide average exposure for the time period during which the workers were employed. This estimated average is approximately 6.5 times as high as the overall average calculated

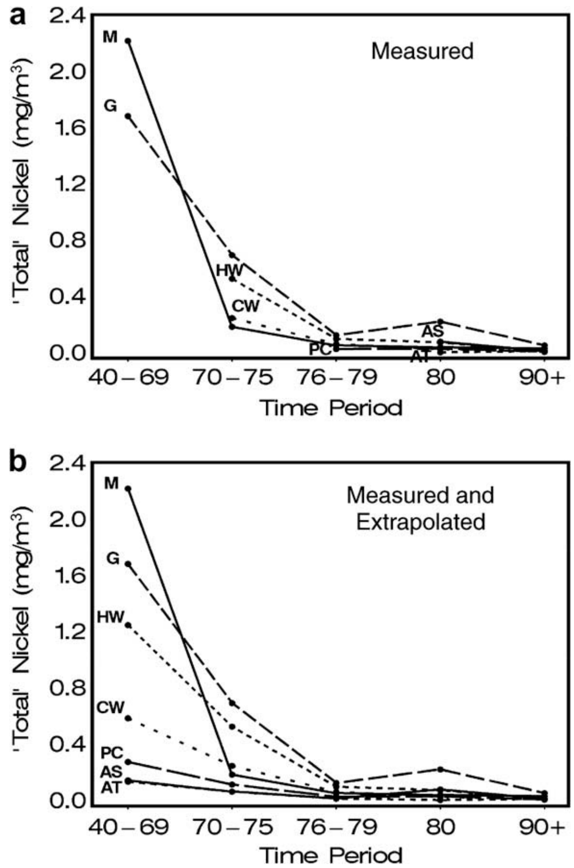


**Fig. 1.** (a) Measured and (b) measured and extrapolated average 'total' nickel concentrations (mg/m$^3$) for work areas in nickel alloy production, 1940 – present: M, melting; G, grinding; CW, cold working; HW, hot working; PC, pickling and cleaning; AT, administrative and technical; AS, allocated services.

from the work area averages provided by Arena et al. (1998). As the latter averages were based almost solely on measurements taken in the late-1970s from one plant, it is not surprising that they are reasonably consistent with the averages of the measurements from the same period and the 1980's that were collected for this paper based upon a number of other plants that participated in the Arena study. There is, however, good evidence that the actual nickel levels to which the cohort members were exposed for the entire time period during which the workers were employed (average ~0.67 mg Ni/m$^3$) were considerably higher than those reported by Arena et al. because the vast bulk of these exposures occurred from the 1940s through the early-1970s, when exposure levels were considerably higher than in the late-1970s. This has implications for what constitutes a "safe" level of occupational nickel exposure in the nickel alloy industry, as discussed below.

## 5. Discussion

The data that have been collected in this effort, as summarized in Table 4 and Fig. 1a and b, provide substantial evidence of a strongly decreasing gradient of airborne nickel levels over time in the nickel alloy industry. It appears that the 1970s constituted a crucial period in the improvement of workers' exposures. As noted above, this is probably due to several factors. As new pollution control technologies became available, a number of companies started to install them in their plants in the mid-1960s through the 1970s. The establishment of the US Occupational Safety and Health Administration (OSHA) and the concomitant setting of enforceable Permissible Exposure Limits (PELs) in the 1970s also spurred companies to further improve their workplace exposure controls, resulting in a more universal use of pollution control technologies such as bag houses, canopy hoods, improved local ventilation, etc. This was confirmed in the narrative materials supplied by a number of the companies. The narrative material also suggested that temporal trends in exposures could be accounted for, in part, by technological changes that improved production processes (e.g., changes to vacuum melting or electro slag remelt furnaces). Failure to adopt new technologies as they became available would result in less competitiveness. Hence, companies were economically motivated to introduce technological changes in a temporally uniform fashion.

It is clear that back-calculations for portions of the exposure time period most relevant to the lung cancer mortality experienced by the cohort (*i.e.*, the 1940s through the mid-1970s) are dependent, in part, on the strength of the impinger data collected from two of the plants in the Arena study. As discussed earlier, impinger data are not without certain limitations. However, as noted by others (e.g., Vincent and Werner, 2003; Vincent, 2007) the potential insight that can be gleaned from past recorded exposures—even when they rely on sampling instrumentation and methods that

**Table 3**
Derivation of multiplicative extrapolation factors and estimation of nickel exposures (mg Ni/m$^3$) where data are unavailable.[a]

| Work area | Multiplicative factor between 1940s–1960s and early-1970s | Multiplicative factor between early-1970s and average for ate-1970s/1980s[b] | Back-extrapolated mean value | 1940s–1960s | Early-1970s | Late-1970s | 1980s | 1990s-Present | Average late-1970s/1980s[b] |
|---|---|---|---|---|---|---|---|---|---|
| Melting | 2.22/0.18 = 12.3 | 0.18/0.04 = 4.5 | N/A | 2.15 | 0.18 | 0.05 | 0.04 | 0.03 | 0.04 |
| Grinding | 1.68/0.69 = 2.4 | 0.69/0.20 = 3.5 | N/A | 1.68 | 0.69 | 0.12 | 0.22 | 0.05 | 0.20 |
| Cold working | 2.4 (estimated)[c] | 0.24/0.03 = 8.0 | 0.24 × 2.4 = **0.58** | **0.58** | 0.24 | 0.06 | 0.02 | <0.01 | 0.03 |
| Hot working | 2.4 (estimated)[c] | 0.52/0.08 = 6.9 | 0.52 × 2.4 = **1.25** | **1.25** | 0.52 | 0.10 | 0.07 | <0.01 | 0.08 |
| Pickling and cleaning | 2.4 (estimated)[c] | 5.7 (estimated)[d] | 0.02 × 5.7 × 2.4 = **0.27**<br>0.02 × 5.7 = **0.11** | **0.27** | **0.11** | 0.02 | 0.03 | <0.01 | 0.02 |
| Administrative and technical | 2.4 (estimated)[c] | 5.7 (estimated)[d] | 0.01 × 5.7 × 2.4 = **0.13**<br>0.01 × 5.7 = **0.06** | **0.13** | **0.06** | **0.01**[e] | <0.01 | 0.01 | 0.01 |
| Allocated services | 2.4 (estimated)[c] | 5.7 (estimated)[d] | 0.01 × 5.7 × 2.4 = **0.14**<br>0.01 × 5.7 = **0.06** | **0.14** | **0.06** | **0.01**[e] | 0.08 | 0.01 | 0.01 |

[a]Estimated nickel exposures that resulted from applying the multiplicative factors are shown in bold for work area/time periods where data were unavailable (shaded cells).
[b]Average for the Late-1970s/1980s is the weighted mean for all measurements taken during those two time periods combined (see Table 2 for weights). The resulting values are shown in the last column of this Table.
[c]Estimated factor derived from the minimum multiplicative factor derived in melting and grinding between the 1940s–1960s and the early-1970s.
[d]Estimated factor derived from the average of multiplicative factors derived in melting, grinding, cold working, and hot working between the early-1970s and the averages for the late-1970s through the 1980s [(4.5 + 3.5 + 8 + 6.9)/4 = 5.7].
[e]Weighted averages for the 1980s to the present were used to extrapolate back to the late-1970s (see Table 2 for weights).

**Table 4**
Nickel exposures for various work areas by time.[a]

| Assumed mean employment years | Percentage of employment exposure | | | | | Weighted average – 10 years employment | Weighted average – 20 years employment | Arena study[b] |
|---|---|---|---|---|---|---|---|---|
| | 1940s/1960s | Early 1970s | Late-1970s | 1980s | 1990s/2000s | | | |
| 10 | 92.4% | 5.8% | 1.8% | 0% | 0% | | | |
| 20 | 79.7% | 13.4% | 3.4% | 3.6% | 0% | | | |
| Work area | "Total" mean nickel exposure (mg Ni/m$^3$) | | | | | | | |
| Melting | 2.22 | 0.18 | 0.05 | 0.04 | 0.03 | 2.05 | 1.79 | 0.083 |
| Grinding | 1.68 | 0.69 | 0.12 | 0.22 | 0.05 | 1.60 | 1.44 | 0.298 |
| Cold working | **0.58** | 0.24 | 0.06 | 0.02 | <0.01 | 0.55 | 0.49 | 0.006 |
| Hot working | **1.25** | 0.52 | 0.10 | 0.07 | <0.01 | 1.19 | 1.07 | 0.111 |
| Pickling and cleaning | **0.27** | **0.11** | 0.02 | 0.03 | <0.01 | 0.26 | 0.23 | 0.008 |
| Administrative and technical | **0.13** | **0.06** | **0.01** | <0.01 | 0.01 | 0.12 | 0.11 | 0.008 |
| Allocated services | **0.14** | **0.06** | **0.01** | 0.08 | 0.01 | 0.13 | 0.12 | 0.071 |
| Average across work areas[c] | **0.73** | **0.25** | **0.05** | 0.12 | 0.02 | 0.70 | 0.63 | 0.101 |

[a] Numbers in bold are back-extrapolated estimates.
[b] These measurements were largely based upon one plant.
[c] Weighted average based on numbers of workers who had ever been employed in the different work areas.

are not as robust as those currently used—can greatly enhance the quality of a retrospective exposure assessment. In this study, efforts have been made to convert particle counts to gravimetric measurements empirically, as opposed to resorting to theoretical computations to derive conversion factors. Also, the narrative material provided for a number of the plants—not just those with impinger measurements—supported the quantitative measurements taken with the impingers, as they describe past operations that often were quite dusty and were noted to have fairly crude ventilation controls. Thus, the impinger data provide an objective component to the efforts to reconstruct historical exposures that otherwise might have been missing.

That said, the largest uncertainty in the present analysis still relates to the back extrapolation of values from later years to the early-1970s and the 1940's through the 1960's. To assess the potential impact of this uncertainty, a sensitivity analysis was conducted in which various assumptions were used to estimate the average nickel level to which the cohort members were exposed (Table 5). As shown in Table 4 and Fig. 1b, the estimated changes occurring between the 1940s through the1960s and early-1970s are based on the extrapolation factors derived from measurements taken in grinding and melting for these periods of time. For reasons discussed above, the smaller of the observed multiplicative factors from these work areas (2.4 in grinding) was used, in combination with another extrapolation factor (5.7), to estimate exposures in work areas/time periods where exposure data were lacking. The underlying assumption in applying these factors was that all changes in exposures other than melting operations were largely due to improvements in pollution control.

However, differing assumptions could be made (Table 5). One such assumption might be that changes in exposures over time could have been due to technological changes as well as to pollution control in work areas in addition to melting. Under this assumption, an average multiplicative factor ($[12.3 + 2.4]/2 \approx 7.4$) could be justified, resulting in an estimated average exposure value for the cohort of 1.20 mg Ni/m$^3$, or approximately 80% higher than the 0.67 mg Ni/m$^3$ estimate obtained using the multiplicative factor of 2.4. Conversely, it might be assumed that apart from melting and grinding operations, dust exposures in other work areas were of the same magnitude in the earliest years of production as in later years—a scenario refuted by the narrative materials describing dusty operations in all production areas in the early years and the expert opinions of hygienists and metallurgists participating in this study. Nevertheless, under this assumption, no temporal trend-based extrapolation would be carried out (*i.e.*, the extrapolated values in the 1940s through the 1960s and early-1970s are assumed to be the same as the averages of measurements from later years) resulting in an estimated cohort-wide average exposure of 0.50 mg Ni/m$^3$. As this is only 25% less than the 0.67 mg Ni/m$^3$ estimate that was obtained with back extrapolation based on trends, it is clear that the use of the trend-based extrapolation factors had an important—but not overwhelming—effect on the estimated average exposure obtained for the cohort. Given the totality of the data available (both quantitative and qualitative) from which to reconstruct historical exposures, the mean of 0.67 mg Ni/m$^3$ is a reasonably conservative "best estimate" of the average across work areas.

It is also worth noting that the changes in exposures over time seen in this study are in good agreement with other analyses of changes in workplace exposures over time. Notably, Symanski et al. (1998) conducted a comprehensive evaluation of long-term changes in occupational exposures among a broad cross-section of industries worldwide. About 700 sets of data from 119 published and several unpublished sources were compiled. This large analysis showed that rates of reduction in workplace exposures

**Table 5**
Sensitivity of estimated nickel exposures to back-extrapolation factor assumptions.

| Back-extrapolation? | Multiplicative back-extrapolation factor between 1940s–1960s and early-1970s | Estimated average "total" nickel exposures (mg Ni/m$^3$) | | |
|---|---|---|---|---|
| | | 10 Years employment | 20 Years employment | Midpoint |
| Yes | 7.4 (average of grinding and melting) | 1.27 | 1.12 | 1.20 |
| Yes | 4.9 (midpoint of average and minimum of grinding and melting) | 0.99 | 0.88 | 0.94 |
| Yes | 2.4 (minimum of grinding and melting) | 0.70 | 0.63 | 0.67[a] |
| Yes | 1.2 (50% of minimum of grinding and melting) | 0.57 | 0.52 | 0.55 |
| No | 0[b] | 0.52 | 0.47 | 0.50 |

[a] Used in derivation of a carcinogenic-based PEL (Appendix A).
[b] Also uses a multiplicative extrapolation factor = 0 between early-1970s and late-1970s/1980s in pickling and cleaning, administrative and technical, and allocated services.

over time showed downward trends ranging from 1% to 62% per year. Most exposures declined at rates between 4% and 14% per year, with a median value of 8%. The estimated changes in exposures in the nickel alloy industry fall well within this range.

### 5.1. Implications for hazard assessment

In assessing the carcinogenic hazards to humans of nickel and its compounds, regulatory and worker/public health evaluation agencies have based their analyses on findings from studies of production workers involved in the processing of nickel sulfide ores. These groups have tended to dismiss studies on nickel workers where excess cancer risks have not been seen—even though these studies are numerous—on the assumption that the cohort size in these latter studies has been too small or the exposures too low, thus, precluding their use as a basis for determining the carcinogenic hazards of various nickel species (IARC, 1990; NTP, 2004). The current study calls that assumption into question.

It is true that nickel exposures in some of the nickel refinery cohorts with excess respiratory cancer risks (e.g., sintering operations in Copper Cliff or Port Colborne, Canada and certain operations in Clydach, Wales before 1930) have been noted to be quite high (>10 mg Ni/m$^3$ for insoluble nickel species, which included nickel subsulfide and >1 mg Ni/m$^3$ for soluble nickel species) (Roberts et al., 1989; ICNCM, 1990; Easton et al., 1992), and, therefore, are not comparable to the nickel concentrations to which the nickel alloy workers studied by Arena et al. were exposed, even in the past. Recent studies of workers employed at Clydach after 1930 (Sorahan and Williams, 2005; Grimsrud and Peto, 2006) have shown modestly elevated lung cancer risks (SMRs of 133–169); however, these results may well be due to cigarette smoking (67% of the refinery workers with known smoking status were smokers) or vestiges of previous high exposures to combinations of sulfidic, oxidic, and/or soluble nickel, which were estimated to be as high as 18, 14, and 2 mg Ni/m$^3$, respectively for periods of time overlapping the employment histories of these workers (Table 2; ICNCM, 1990). Thus, neither past nor present studies of Clydach workers, nor studies of Copper Cliff or Port Coborne workers provide a useful comparison to the nickel alloy workers.

By contrast, roasting and smelting workers in Norway (Grimsrud et al., 2000, 2003) or workers employed at the Coniston sinter plant in Sudbury, Canada (ICNCM, 1990) do provide a reasonable comparison. In both instances, past exposures to metallic and oxidic nickel species—the only two insoluble nickel species to which nickel alloy workers would be exposed—have been reported to be roughly similar to past exposures in the nickel alloy industry: ≈0.1–4 mg Ni/m$^3$ in the aforementioned roasting, smelting, or sintering workers (see Table 1, Grimsrud et al., 2003 and Table 9, ICNCM, 1990) versus 0.1–2 mg Ni/m$^3$ in the alloy workers. Yet, the nickel alloy workers displayed no evidence of occupationally-related lung cancers, whereas the roasting, smelting, and sintering workers did.

The reason for this discrepancy in lung cancer mortality may lie in the type and mix of nickel species and other carcinogenic agents to which the workers were exposed. In this regard, metallic nickel has not been found to be carcinogenic either in nickel-producing or -using workers (ICNCM, 1990; Sivulka, 2005). In particular, workers in barrier manufacturing and powder metallurgy where exposures have been solely to metallic nickel at average concentrations ranging from 0.1 to 1.5 mg Ni/m$^3$ had no excess respiratory cancer risks (Cragle et al., 1984; Sivulka, 2008). Also, a recent chronic inhalation bioassay showed no evidence of lung cancer in Wistar rats dosed with metallic nickel (Oller, 2008). Therefore, it does not appear that metallic nickel is a respiratory carcinogen. This suggests that the US OSHA's existing PEL of 1.0 mg Ni/m$^3$ for metallic nickel is adequately protective against any respiratory cancer risk.

The situation with respect to "oxidic" nickel is more complicated. Most of the oxidic nickel to which workers in the "high risk" cohorts were exposed was in the form of nickel-copper oxides; this was certainly the case in the aforementioned Norwegian roasting and smelting workers. But this would not have been the case for nickel alloy workers who are, with a few exceptions, exposed to a purer high-temperature nickel oxide devoid of copper. Given that the nickel alloy workers did not show evidence of occupationally-related lung cancers whereas the Norwegian workers did at comparable concentrations of oxidic nickel, it would not be unreasonable to speculate that the difference in lung cancer risk may have been due, in part, to the specific oxidic compound(s) to which the workers were exposed. While a high-temperature nickel oxide devoid of copper has shown "some" evidence of carcinogenicity in a chronic inhalation bioassay of F344 rats, it was not particularly potent; nor was it carcinogenic in mice (NTP, 1996). In contrast, nickel-copper oxides have been shown to be much more reactive and carcinogenic than high-temperature nickel oxides in several studies (Benson et al., 1988; Sunderman et al., 1990), lending credence to the hypothesis originally proposed by the ICNCM that the type of oxidic nickel to which workers are exposed may be critical to the elicitation of a carcinogenic response. This is supported by the absence of evidence of excess cancer risks in nickel-producing workers processing lateritic ores where—like most alloy workers—exposures to oxidic nickel are devoid of copper (Goldberg et al., 1987, 1994; Cooper and Wong, 1981; ICNCM, 1990).

It should also be noted, however, that—unlike the alloy workers—the Norwegian roasting and smelter workers were also exposed to soluble and sulfidic nickel, the former of which is suggested by Grimsrud et al. to have played a significant role in the excess cancer risks seen in the roasting and smelter workers. Although nickel exposures to insoluble metallic and oxidic species were comparable between these two groups of nickel workers from different nickel industry sectors, their exposures to nickel subsulfide and soluble nickel were not. Thus, as noted above, differences in carcinogenic risk may have been due to the form of oxidic nickel present and/or the more complex mixtures of nickel species (and possibly other confounding factors) that were present in the roasting and smelting environments, but absent in the nickel alloy plants.

In the case of the Coniston sinter plant in Canada where nickel–copper oxides—although present—would have been at lower concentrations than in Norway, other carcinogenic agents (e.g., arsenic) were present in the ores being processed. This is not the case in nickel alloy working environments.

An understanding of the fundamental differences between primary nickel and nickel alloy production is important to evaluating potential differences in health hazards and risks for these industrial sectors. Nickel production from ores entails complex and unique processes in which feed materials vary greatly (Boldt, 1967; ICNCM, 1990). As a consequence, variability seen in nickel species across time and work areas is often due to changes in these materials and processes, as well as improvements in workplace conditions. In particular, workers processing sulfidic ores are exposed to a wide variety of nickel species, including nickel sulfides, nickel-copper oxides, black and green nickel oxides, nickel carbonate, nickel hydroxide, nickel chlorides and sulfates, to name just a few. The other metals in the ore and chemicals and processes required to extract nickel from the ore also are numerous and varied (e.g., arsenic, cobalt, inorganic acid mists).

In contrast, the production methods used in alloy production and fabrication plants are fairly generic. They start with a "purer" feedstock—generally metallic nickel, nickel alloy scrap or, occasionally, a high-temperature nickel oxide—that is melted and reduced at high temperatures with other metals. Most feedstocks are in massive form, but if stored in drums, the entire drum is thrown into the furnace for melting. Once this process is completed, there are only so many ways to cold or hot work a nickel alloy or to grind a bar. The practices used are universal to almost all alloy companies and fabricators. Differences in exposures between alloy companies will be due mainly to the alloys they make and the inherent dustiness of their operation. Related nickel exposures will be simpler and more homogeneous than those encountered in the processing of sulfidic ores.

This suggests that an "industry sector effect" may be operative in eliciting respiratory cancers in workers where sulfidic ores are processed (Sivulka et al., 2007). Others also have noted a "process dependency" for the risk of respiratory cancers among such workers and have speculated that this may account for why animal studies—where exposures are to single forms of pure nickel species—cannot simulate the very complex mixes of nickel compounds and substances found in such operations (Neiboer et al., 2005). This is not to say that animal data should be ignored in assessing potential nickel-related cancer risks. But it does emphasize the importance of focusing on the specific "mix" of substances that have caused cancers in certain nickel workers, as this mix may not be found in other work environments where nickel exposure occurs. Greater attention to this "mix" of exposures is particularly appropriate when evaluating the "sufficiency" of the human evidence for the carcinogenicity of specific nickel species, since all the studies finding a significantly increased cancer risk involve nickel workers processing sulfidic ores—a point that must be kept in mind when evaluating the evidence for human carcinogenicity of different nickel species.

### 5.2. Implications for risk assessment

The newly reconstructed exposures within the nickel alloy industry also have implications for carcinogenic risk assessments and the concomitant setting of Permissible or Occupational Exposure Limits (PELs or OELs). In many jurisdictions, a single exposure limit for all insoluble forms of nickel has been derived. Many of these limits are in the range of 0.1 to 1 mg $Ni/m^3$ "total" nickel; a number of them apply not only to metallic and oxidic species of nickel, but also to sulfidic nickel. As discussed above, sulfidic nickel (shown to be carcinogenic in both animal and human studies) is very unlikely to be present in the nickel alloy industry, whereas metallic nickel and oxidic nickel will. Table 4 indicates that, taking account of changes over time, the estimated average exposure to insoluble nickel species of alloy workers in the cohort studied by Arena et al. was 0.67 mg $Ni/m^3$ "total" nickel, and many of these workers experienced much higher exposures on a daily basis in the period from 1940 through the 1960s; yet they showed no statistically significant evidence of increased respiratory cancer risk.

Simplistically, the exposures seen in Table 4 can, therefore, be viewed as those associated with a No Observed Adverse Effect Concentration (NOAEC) for carcinogenicity in this cohort.

Appendix A shows alternative ways of deriving carcinogenicity-based PELs for nickel alloy workers. To some extent, it reflects the diversity in the methods used by various regulatory authorities to establish workplace exposure limits (Haber and Maier, 2002). Depending on the approach taken and the degree of conservatism applied, PELs derived from the reconstructed exposures for the nickel alloy workers range from approximately 0.5 to 2 mg $Ni/m^3$ "total" nickel based upon the best estimate for the insoluble species of nickel to which alloy workers are exposed (*i.e.*, 0.67 mg $Ni/m^3$ "total" insoluble nickel). From Appendix A, it appears that a carcinogenicity-based PEL of around 0.5 mg $Ni/m^3$ (or possibly somewhat higher) would be a reasonably conservative exposure limit if the goal is to ensure that alloy workers are not subjected to a nickel-related increased respiratory cancer risk greater than 1/1000 over the course of a working lifetime.

## 6. Summary

In summary, this study has shown that through careful canvassing of available sources of information and proper attention to analytical considerations it is possible to reconstruct historical exposures in an industry sector for which past exposures have not been reported. This kind of effort is clearly worthwhile, as the reconstructed exposure values can provide critical information for appropriate, scientifically defensible assessments of hazard and risk. Reconstruction of historical exposures in the nickel alloy industry has shown that exposures were, indeed, higher in the past than in the present—a belief that is widely held in the scientific community but has, until recently, generally been unproven with respect to long-term trends in occupational exposures (Symanski et al., 1998). Moreover, quantitative estimates of these past exposures provide valuable insight into the nature of the carcinogenic hazards and risks associated with exposures to nickel in the alloy industry.

This study suggests that carcinogenicity-based occupational exposure limits for the nickel alloy industry could reasonably be set at 0.5 mg $Ni/m^3$ "total" insoluble nickel (or possibly higher), at least for the insoluble nickel species to which alloy workers are exposed. This would be roughly equivalent to 1 mg $Ni/m^3$ inhalable insoluble nickel. Insoluble species-specific OELs for the nickel alloy industry could also be derived, as proposed by Sivulka et al. (2007), but this would require additional speciation sampling within the industry. Such sampling, in conjunction with an analysis of the cohort by cumulative exposure to different nickel species, could potentially provide a more definitive understanding of carcinogenic risks, if any, associated with exposure to oxidic nickel at the levels experienced by nickel alloy workers.[3] Thus, to some extent, the above analyses may be viewed as being preliminary in nature. Regardless of whether or not such species-specific OELs are set, this study raises serious questions about the scientific justification for applying exposure limits based on data from "high risk" nickel-production cohorts to the nickel alloy industry—or, for that matter, possibly to other nickel industry sectors where the nickel species present are far more homogeneous than (and significantly different from) the mix of nickel species and other substances found in producing industries where sulfidic nickel ores are refined.

## Acknowledgments

This work was supported by Vale Inco Americas, Inc. The authors wish to thank Ken Money, Ron Simonton, Bruce Conard, Neil King, and Adriana Oller for graciously giving of their time in reviewing the overall manuscript. Valuable support services were provided by Diane Baksa. We would also like to thank the nickel alloy producers and fabricators within the U.S. who generously provided the exposure information presented in this paper and whose personnel lent invaluable insight on matters concerning industrial hygiene and past operations. This manuscript represents the individual professional views of the authors and not necessarily the views of the companies or the individuals acknowledged above.

[3] To this end, if species-specific OELs for oxidic nickel within the nickel alloy industry are derived by the regulatory community, it would be instructive to derive a carcinogenicity-based OEL on the basis of the animal data for comparative purposes.

## Appendix A. Scientific considerations and adjustments in deriving a carcinogenicity-based PEL using reconstructed exposures in the US nickel alloy industry

### *A.1. Adjustment for workplace and temporal variability*

Tables 2 and 4 show that there were large systematic differences among workplaces, as well as substantial random variability within them. While, on the face of it, it might seem appropriate to set a carcinogenicity-based PEL for the alloy workers at the cohort's overall average exposure level (0.67 mg/m$^3$ "total" insoluble nickel), this would be somewhat illogical, as work areas with average exposures above this level would be viewed as "unsafe." For example, the more than 14,000 workers ever employed in grinding, melting, and hot working, where average exposures ranged from approximately 1 to 2 mg Ni/m$^3$, would not be considered to be properly protected, even though these workers showed no evidence of occupationally-related excess lung cancer risk. Based on exposure and cancer mortality data from these workers, it could be argued that a PEL in the range of 1 to 2 mg/m$^3$ "total" insoluble nickel would be protective of all workers and that 0.67 mg/m$^3$ might constitute an overly conservative PEL.

An estimated carcinogenicity-based PEL in the range of 1 to 2 mg Ni/m$^3$ "total" insoluble nickel can also be supported on the basis of temporal variability. In establishing a "safe" PEL across time, it is logical to take into account the overall statistical distribution of 8-h measurements that contribute to the long-term mean values. As a consequence, the PEL for any given workplace could reasonably be set at a level greater than the mean value that reflects this day to day variation. Table 2 shows the estimated 95th percentiles of the temporal distributions of work area measurements in the late-1970s to the present to be 2.3–6.2 (average = 3.8) times higher than the observed mean values. And while 95th percentiles could not be directly computed for periods prior to the late-1970s, the ratios of the largest of the individual mean values (designated with a superscript of "m" in Table 2) to the overall mean ranges within work areas are between 1.5 and 15 (average = 4.7). Based on this level of variability, it is reasonable to assume that the 95th percentile of the distribution of daily exposures was at least three times larger than the overall cohort-wide average of 0.67 mg Ni/m$^3$ (*i.e.*, 1.95 $\approx$ 2.0 mg Ni/m$^3$). Thus, a carcinogenicity-based PEL for insoluble nickel species to which nickel alloy workers are exposed could arguably be set at 2.0 mg Ni/m$^3$ "total" nickel (or higher), as this would bound the 95th percentile of the probability distribution of daily exposures for these nickel alloy workers whose long-term mean exposure was 0.67 mg Ni/m$^3$.

### *A.2. Adjustment for length of employment*

In constructing a PEL for cancer, it is generally assumed that risk is proportional to cumulative exposure (average exposure $\times$ years of exposure). As it has been noted that most of the alloy workers did not spend their entire working careers in this industry, an adjustment for uncertainty in length of employment could also be factored into risk calculations. A reasonable estimate of the cohort's average length of employment is 10 years. Assuming that carcinogenic risk increases linearly with cumulative exposure, a downward adjustment factor of four to account for exposure over a 40-year working career might be applied to an exposure limit adjusted for temporal and workplace variability, resulting in a carcinogenicity-based PEL of 0.5 mg Ni/m$^3$ "total" insoluble nickel (2.0/4 = 0.5).

### *A.3. Consideration of the level of risk*

PELs based on cancer are often set at a level that assures that a worker's average exposure concentration does not exceed a value that is associated with some predetermined level of acceptable excess risk (*i.e.*, risk in excess of that which occurs in unexposed individuals). Typically, this "bright line" for acceptable excess risk in a workforce has been set at 1 cancer case in 1000 workers (<1/1000) (US OSHA, 1996, 1997). There was no substantive evidence of excess risk in this very large cohort (observed relative risk = 1.01). Under the assumption that the small observed increase in risk is real, the excess risk would be $6 \times 10^{-4}$, based on a 6% background lifetime lung cancer risk in US white males (Merrill, 2000). That is: Excess risk = $(1.01-1) \times 0.06 = 6 \times 10^{-4}$. Thus, no adjustment factor would be needed for a carcinogenicity-based PEL of 0.5 mg Ni/m$^3$ "total" insoluble nickel which would limit risk to <1/1000 in workers with 40 years of exposure.

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