Safe Use of Nickel in the Workplace

Third Edition, Incorporating European Nickel Risk Assessment Outcomes

A Guide for Health Maintenance of Workers Exposed to Nickel, Its Compounds and Alloys

HEALTH GUIDE

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1. About This Guide

Investigation into the toxicological effects of nickel salts on animals was first reported in 1826. Since that time, numerous reports and papers have been generated on the human health and environmental effects of nickel. The reported effects of nickel and its compounds on humans are wide ranging, comprising effects that are both beneficial (the probable essentiality of nickel in humans) as well as harmful (skin allergy and, in certain circumstances, respiratory cancer). Although nickel has been studied extensively, there is still much to be learned about this ubiquitous metal. Given the importance of nickel to industrialized societies, a guide to evaluating workplace exposures has long been needed. The first edition of such a guide was prepared in 1993 by the Nickel Producers Environmental Research Association (NiPERA) in collaboration with the Nickel Development Institute (now the Nickel Institute). Additional assistance for the first edition was provided by the Radian Corporation. The second edition of the Guide was published in 1997. Subsequent to that printed edition, the Guide was published online and was subject to revisions in 2002 and 2004. The current version of this Guide is the third printed version and reflects the evolving nature of the knowledge about the health concerns associated with working with nickel and its compounds.

This Guide has been written for those individuals who are responsible for the health maintenance of workers exposed to nickel, its compounds, and alloys. As such, it is directed to a variety of individuals including operational managers, business managers, industrial hygienists, occupational health nurses, physicians, joint occupational health and safety committees, and other health professionals. Its purpose is not only to educate the reader about the potential hazards associated with exposure to various forms of nickel but also to instruct the reader in the safe handling of nickel-containing substances in the workplace. Like all scientific documents, the information contained within this Guide constitutes a "snapshot" and is subject to change as knowledge is gained about nickel. Further up-dates are planned.

Certain conventions have been followed in preparing this Guide. Since it mainly addresses the health effects associated with occupational exposure to nickel and nickel-containing substances, evaluations are based predominantly on epidemiological and clinical studies. Most evaluations are qualitative and reflect the overall weight-of-evidence reported from studies of nickel workers. Discussions of the health effects related to working with nickel compounds focus on specific forms of nickel. Because they are not present in most work environments, organic nickel compounds, with the exception of a brief discussion on the acute toxicity of nickel carbonyl, are not discussed within this Guide. Finally, unless noted otherwise, statements regarding the "solubility" of nickel compounds are made with respect to their solubility in biological fluids as opposed to water.

The Guide has been organized into a summary of the Guide followed by sections on production, sources of exposure, pharmacokinetics, toxicology, health surveillance, exposure levels and air monitoring, control measures, and hazard communication. Additional instructional materials are provided in appendices.

1.1 Summary

Nickel is a naturally occurring element that exists in nature mainly in the form of sulfide, oxide,

1. About This Guide

and silicate minerals. Because it is ubiquitous, humans are constantly exposed to nickel in various amounts. "Zero exposure" to nickel is neither possible nor desirable. Nickel has been shown to be an essential element in certain micro-organisms, animals, and plants. The generally held view is that nickel is probably an essential element for humans as well.

Nickel is an extremely important commercial element. Factors which make nickel and its alloys valuable commodities include strength, corrosion resistance, high ductility, good thermal and electric conductivity, magnetic characteristics, and catalytic properties. Stainless steels are particularly valued for their hygienic properties. In some applications, nickel alloys are essential and cannot be substituted with other materials. Given these many beneficial properties, nickel is used in a wide variety of products discussed below.

1.2 Production and Use

Nickel in one form or another has literally hundreds of thousands of individual applications. Annual world production of nickel products in recent years has averaged in excess of 1,100 kilotonnes. Primary nickel products are classified by the amount of nickel they contain. Class I products contain almost 100 percent nickel, whereas Class II products vary widely in their nickel content.

Most primary nickel is used in alloys, the most important of which is stainless steel. Other uses include electroplating, foundries, catalysts, batteries, welding rods, coinage, and other miscellaneous applications. The list of end-use applications for nickel is, for all practical purposes, limitless. Nickel is found in transportation products, electronic equipment, chemicals, construction materials, petroleum products, aerospace equipment, durable consumer goods, paints, and ceramics. From this list, it is evident that nickel is a critical metal to industrialized societies.

1.3 Sources of Exposure

Given its many uses and applications, the potential for exposure to nickel, its compounds, and alloys is varied and wide ranging. With respect to occupational exposures, the main routes of toxicological relevance are inhalation and, to a lesser extent, skin contact.

Workers engaged in nickel production – which may include mining, milling, concentrating, smelting, converting, hydrometallurgical processes, refining, and other operations – are exposed to a variety of nickel minerals and compounds depending upon the type of ore mined and the processes used to produce intermediate and primary nickel products. Generally, exposures in the producing industry are to moderately soluble and insoluble forms of nickel. In the producing industry, soluble nickel compounds are more likely to be found in hydrometallurgical operations. Exposures in nickel-using industry sectors vary according to the products produced and include both soluble and relatively insoluble forms of nickel.

In the past, airborne occupational nickel concentrations were believed to have been quite high (>10 mg Ni/m^3) in certain producing operations, with some estimates of exposures as high as 100 mg Ni/m^3 or more for Ni_3S_2 sintering (sometimes referred to as "matte" sintering). More recent estimates of exposure (post-1960)

are much lower, with current measurements generally averaging <1 mg Ni/m^3. Exposures to nickel species in user industries have historically been much lower than in producing industries, with estimates generally averaging well below 1 mg Ni/m^3.

1.4 Pharmacokinetics of Nickel

The major routes of nickel intake are dietary ingestion and inhalation. In most individuals, diet constitutes the main source of nickel intake. Recent studies indicate that average dietary intake is approximately 0.16 mg Ni/day. Nickel in drinking water (averages ranging from <0.001 to 0.01 mg Ni/L) and ambient air (averages ranging from 1 to 60 ng Ni/m^3) is generally quite low. Other sources of nickel exposure include contact with nickel-containing articles such as jewelry, medical applications, and tobacco smoke.

For individuals occupationally exposed, total nickel intake is likely to be higher than that of the general populace. Whether diet or workplace exposures constitute the main source of nickel in workers depends upon a number of factors. These factors include the aerodynamic size of the particles and whether the particles are inhalable, the concentration of the nickel that is inhaled, the minute ventilation rate of a worker, whether breathing is nasal or oronasal, the use of respiratory protection equipment, personal hygiene practices, and general work patterns.

Toxicologically speaking, inhalation is the most important route of nickel exposure in the workplace, followed by dermal exposure. Deposition, absorption, and retention of nickel particles in the respiratory tract will depend on many of the factors noted above for intake. Not all particles are inhalable. Humans inhale only about half of the particles with aerodynamic diameters >30 µm, and it is believed that this efficiency may decline rapidly for particles with aerodynamic diameters between 100 and 200 µm. Of the particles inhaled, only a small portion with aerodynamic diameters larger than 10 µm are deposited in the lower regions of the lung, with deposition in this region predominantly limited to particles ≤4 µm.

Factors such as the amount deposited, solubility, and surface area of the particle will influence the behavior of particles once they are deposited in the lung. The smaller and more soluble the particle, the more rapidly it will be absorbed into the bloodstream and excreted. The residence time of nickel-containing particles in the lung is believed to be an important component of toxicity.

With respect to skin absorption, divalent nickel has been shown to penetrate the skin fastest at sweat ducts and hair follicles; however, the surface area of these ducts and follicles is small. Hence, penetration through the skin is primarily determined by the rate at which nickel is able to diffuse through the horny layer of the epidermis. Although the actual amount of nickel permeating the skin from nickel-containing materials is unknown, in studies using excised human skin, the percent permeation was small, ranging from 0.23 (non-occluded skin) to 3.5 percent (occluded skin) of an administered dose of nickel chloride. Marked differences in the rate of nickel permeation have been reported for nickel solutions, with nickel sulfate solutions permeating the skin at a rate 50 times slower than nickel chloride solutions.

Analyses of human tissues from autopsy studies have shown highest concentrations of nickel in the lungs, thyroid gland, and adrenal gland, followed by lesser concentrations in kidney, liver, heart, spleen, and other tissues. Excretion of absorbed nickel is mainly through urine, whereas unabsorbed nickel is excreted mainly in feces. Nickel also may be excreted in sweat, hair, and human breast milk.

1.5 Summary of the Toxicity of Nickel Compounds

Just as the pharmacokinetics of chemical nickel species are influenced by their physical and chemical properties, concentration and route of exposure, so too are the toxic effects of nickel. Although a number of nickel-related effects, including renal and reproductive effects, have occasionally been reported, the main effects noted in humans are respiratory and dermal. Consequently, the major routes of toxicological relevance in the workplace are inhalation and skin contact.

In most work environments, the potential chronic toxicity of various nickel species is likely to be of more concern than acute effects, with the exception of nickel carbonyl. Long-term exposures to some nickel compounds have been associated with excess lung and nasal sinus cancers. The major source of evidence for this association comes from studies of workers who were employed in certain nickel-refining operations. On the whole, these workers were generally exposed to higher concentrations of nickel than those that prevail in many workplaces today. These workers were also exposed to a variety of other potentially carcinogenic substances, including arsenic compounds, polyaromatic hydrocarbons (PAHs), and sulfuric acid mists. These concurrent exposures make a direct-cause-and-effect interpretation of the data difficult, although in some instances, the animal data help to shed light on the potential carcinogenic role, if any, played by different nickel species. Summarized below are the respiratory and dermal effects associated with exposure to individual nickel species.

1.5.1 Summary of the Toxicity of Metallic Nickel

A determination of the health effects of metallic nickel is based mainly upon epidemiological studies of over 40,000 workers from various nickel-using industry sectors (nickel alloy manufacturing, stainless steel manufacturing, and the manufacturing of barrier material for use in uranium enrichment). These workers were examined for evidence of carcinogenic risk due to exposure to metallic nickel and, in some instances, accompanying oxidic nickel compounds and nickel alloys. No nickel-related excess respiratory cancer risks have been found in any of these workers. Animal data on carcinogenicity are in agreement with the human data. A recent regulatory-compliant study on the inhalation of metallic nickel powder was negative for carcinogenicity. However, at levels above 0.1 mg Ni/m^3, chronic respiratory toxicity was observed in the animals.

Data relating to respiratory effects associated with short-term exposure to metallic nickel are very limited. One case report of a fatality has been recorded in a man spraying nickel using a thermal arc process. However, the relevance of the case is questionable since the reported expo-

sure to total nickel was extremely high (382 mg Ni/m^3). Nevertheless, special precautions to reduce inhalation exposure to fine and ultrafine powders should be taken.

Collectively, animal and human data present a mixed picture with respect to the potential role that metallic nickel may play in non-malignant respiratory disease. A few cases of asthma or fibrosis have been reported in humans and certain inflammatory effects have been noted in animals. However, the overall literature shows that past exposures to metallic nickel have not resulted in excess mortality from such diseases. Additional studies on such effects would be useful.

Skin sensitization to nickel metal can occur wherever there is leaching of nickel ions from articles containing nickel onto exposed skin. Occupational exposures involving direct and prolonged skin contact with metallic nickel may elicit cutaneous allergy (allergic contact dermatitis) in nickel-sensitized workers. However, nickel dermatitis occurs mainly as the result of non-occupational exposures.

1.5.2 Summary of Nickel Metal Alloys

Each type of nickel-containing alloy is a unique substance with its own special physico-chemical and biological properties that differ from those of its individual metal constituents. The potential toxicity of a nickel alloy (including carcinogenic effects) must, therefore, be considered separately from the potential toxicity of nickel metal itself and other nickel-containing alloys.

While there are no studies of nickel workers exposed solely to nickel alloys in the absence of metallic or oxidic nickel, studies on stainless steel and nickel alloy workers (who would likely have low level nickel alloy exposures) suggest an absence of nickel-related excess cancer risk. Intratracheal studies on animals have generally shown an absence of cancer risk in animals exposed to nickel alloys. Collectively, these studies suggest that nickel alloys do not act as respiratory carcinogens. For many alloys, this may be due to their corrosion resistance which results in reduced releases of metal ions to target tissues.

With respect to non-carcinogenic respiratory effects, no animal data are available for determining such effects, and the human studies that have looked at such endpoints have generally shown no increased mortality due to non-malignant respiratory disease.

Because alloys are specifically formulated to meet the need for manufactured products that are durable and corrosion resistant, an important property of all alloys and metals is that they be insoluble in aqueous solutions. They can, however, react (corrode) in the presence of other media. Of particular importance to dermal exposures is the potential of individual alloys to corrode in sweat. The potential for nickel alloys to elicit an allergic reaction in occupational settings will depend on both the sweat resistant properties of the alloy and the amount of time a worker is in direct and prolonged skin contact with an alloy. Alloys that release less than 0.5 µg/cm^2/week are generally believed to be protective of the majority of nickel-sensitized individuals when in direct and prolonged skin contact. Alloys that release greater than 0.5 µg/cm^2/week of nickel may not, in and of themselves, be harmful. They may be used safely when not in direct and prolonged contact with the skin or when appropriate protective clothing is worn.

1.5.3 Summary of the Toxicity of Soluble Nickel

European regulatory activity in the first decade of the new millennium has resulted in soluble nickel compounds being classified as human inhalation carcinogens. However, the precise role of soluble nickel in human carcinogenicity is still uncertain. Epidemiologic information suggests that an increased risk of respiratory cancer associated with refinery process exposure to soluble nickel compounds primarily occurs at levels in excess of 1 mg Ni/m^3. However, a few recent studies have noted that exposures slightly lower than this (around 0.5 mg Ni/m^3) may have been associated with the excess respiratory cancers observed in workers exposed to soluble nickel.

Well-conducted inhalation animal studies where rats and mice were exposed to soluble nickel at workplace equivalent concentrations up to 2-6 mg Ni/m^3 did not show any evidence of carcinogenicity. However, at workplace equivalent levels above 0.1 mg Ni/m^3, chronic respiratory toxicity was observed. Respiratory toxicity due to soluble nickel exposures may have enhanced the induction of tumors by less soluble nickel compounds or other inhalation carcinogens seen in refinery workers. This mode of action is in agreement with mechanistic information indicating that nickel ions from soluble nickel compounds will not be bioavailable at target respiratory nuclear sites because they have inefficient cellular uptake and are rapidly cleared from the lungs.

With respect to non-malignant respiratory effects in humans, the evidence for soluble nickel salts being a causative factor for occupational asthma, while not overwhelming, is more suggestive than it is for other nickel species. Such evidence arises mainly from a small number of case reports in the electroplating industry and nickel catalyst manufacturing. It should be noted, however, that exposure to soluble nickel can only be inferred in some of the cases and confounding factors (exposure to chromium, cobalt, and plating solutions of low pH) often have not been taken into account.

Aside from asthma, the only other non-carcinogenic respiratory effect reported in nickel workers exposed to soluble nickel is that of fibrosis. Evidence that soluble nickel may act to induce pulmonary fibrosis comes from a recent study of nickel refinery workers that showed modest abnormalities in the chest X-rays of workers. An association between the presence of irregular opacities (ILO[1] ≥1/0) in chest X-rays and cumulative exposures to soluble nickel, sulfidic nickel, and possibly metallic nickel, was reported. The significance of these results for the clinical diagnosis of fibrosis remains to be determined.

Historically, workplaces where prolonged contact with soluble nickel has been high, have shown high risks for allergic contact nickel dermatitis. For example, nickel dermatitis was common in the past among nickel platers. Due to improved industrial and personal hygiene practices, however, over the past several decades, reports of nickel sensitivity in workplaces, such as the electroplating industry, have been sparse.

[1] *Based on a chest radiographs from the International Labor Organization (ILO) set of standard chest X-rays.*

1.5.4 Summary of the Toxicity of Oxidic Nickel

As with above-mentioned species of nickel, the critical health effect of interest in relation to occupational exposure to oxidic nickel is respiratory cancer. Unlike metallic nickel, which does not appear to be carcinogenic in humans or animals, and soluble nickel, whose carcinogenic potential currently appears to be the opposite in humans and animals, the evidence for the carcinogenicity of certain oxidic nickel compounds is more compelling. That said, there is still some uncertainty regarding the forms of oxidic nickel that induce tumorigenic effects. Although oxidic nickel is present in most major industry sectors, it is of interest to note that epidemiological studies have not consistently implicated all sectors as being associated with respiratory cancer. Indeed, excess respiratory cancers have been observed only in refining operations in which nickel oxides were produced during the refining of sulfidic ores and where exposures were relatively high (>5 mg Ni/m^3). At various stages in this process, nickel-copper oxides may have been formed. In contrast, no excess respiratory cancer risks have been observed in workers exposed to lower levels (<2 Ni/m^3) of oxidic nickel free of copper during the refining of lateritic ores or in the nickel-using industry.

A high calcining temperature nickel oxide administered to rats and mice in a two-year inhalation study did show some evidence of carcinogenicity in rats. In intraperitoneal studies, nickel-copper oxides have appeared to be as potent as nickel subsulfide in inducing tumors at injection sites. There is, however, no strong evidence to indicate that black (low temperature) and green (high temperature) nickel oxides differ substantially with regard to tumor-producing potency.

There is no single unifying physical characteristic that differentiates oxidic nickel compounds with respect to their *in vitro* genotoxicity or carcinogenic potential. Some general physical characteristics which may be related to carcinogenicity include: particle size ≤5 µm, large particle surface area, presence of metallic or other impurities and/or amount of Ni (III), and the ability to induce reactive oxygen radicals. Phagocytosis appears to be a necessary, but not sufficient condition for carcinogenesis. Solubility in biological fluids will also affect how much nickel ion is delivered to target sites (*i.e.,* cell nucleus).

With respect to non-malignant respiratory effects, oxidic nickel compounds do not appear to be respiratory sensitizers. Based upon numerous epidemiological studies of nickel-producing workers, nickel alloy workers, and stainless steel workers, there is little indication that exposure to oxidic nickel results in excess mortality from chronic respiratory disease. In the few instances where excess risks of non-malignant respiratory disease did appear – for example, among refining workers in Wales – the excesses were seen only in workers with high nickel exposures (>10 mg Ni/m^3), in areas that were reported to be very dusty. With the elimination of these dusty conditions, the risk that existed in these areas seems largely to have disappeared by the 1930s. In two studies of nickel workers using lung radiographs, there was no evidence that oxidic nickel dusts caused a significant fibrotic response.

Dermal exposures to oxidic nickel are believed to be of little consequence to nickel workers. While no data are directly available on the effects of oxidic nickel compounds on skin, little skin absorption of nickel ions is expected due to their low water solubility.

1.5.5 Summary of the Toxicity of Sulfidic Nickel

Of all the nickel species examined in this document, a causal relationship for respiratory cancer can best be established for nickel subsulfide. The human data suggest that respiratory cancers have been primarily associated with exposures to less soluble forms of nickel (including sulfidic nickel) at concentrations in excess of 10 mg Ni/m^3. Animal data unequivocally point to nickel subsulfide as being carcinogenic.

Relative to other nickel compounds, nickel subsulfide may be the most efficient at inducing the heritable changes needed for the cancer process. *In vivo*, nickel subsulfide is likely to be readily phagocytized and dissolved by respiratory epithelial cells resulting in efficient delivery of nickel (II) to the target site within the cell nucleus. In addition, nickel subsulfide has relatively high solubility in biological fluids. This results in the release of nickel (II) ions, with subsequent induction of cell toxicity and inflammation. Chronic cell toxicity and inflammation may enhance tumor formation by nickel subsulfide or other carcinogens (as discussed for soluble nickel compounds).

The evidence for non-malignant respiratory effects in workers exposed to sulfidic nickel has been mixed. Mortality due to non-malignant respiratory disease has not been observed in Canadian sinter workers, but has in refining workers in Wales. With the elimination of the very dusty conditions that likely brought about such effects, the risk of respiratory disease disappeared in the Welsh workers by the 1930s. In a recent study of Norwegian nickel refinery workers, an increased risk of pulmonary fibrosis was found in workers with cumulative exposure to sulfidic and soluble nickel. The significance of these results for the clinical diagnosis of fibrosis remains to be determined.

No relevant studies of dermal exposure have been conducted on workers exposed to sulfidic nickel. Likewise, no animal studies have been undertaken.

1.5.6 Summary of the Toxicity of Nickel Carbonyl

The human data unequivocally show that nickel carbonyl is an agent which is extremely toxic to man; the animal data are in agreement with respect to this acute toxicity.

It is not possible to assess the potential carcinogenicity of nickel carbonyl from either human or animal data. Unless additional, long-term carcinogenicity studies in animals can be conducted at doses that do not exceed the Maximum Tolerated Dose (MTD) for toxicity, the database for the carcinogenicity of nickel carbonyl will remain unfilled. This issue may only be of academic interest since engineering controls and close monitoring of nickel carbonyl exposure to prevent acute toxicity greatly limit possible exposures to this compound.

Exposures to nickel carbonyl are usually confounded with exposures to other nickel compounds. However, for acute nickel carbonyl exposures urinary nickel can be used as a health guidance value to predict health effects and the need for treatment. Reasonably close correlations between the clinical severity of acute poisoning and urinary concentrations of nickel during the

initial three days after exposure have been established as follows:

Symptoms	18-hr urine specimen (µg Ni/l)
Mild	60-100
Moderate	100-500
Severe	>500

These values, however, are only relevant when urinary nickel is not elevated due to other nickel compound exposures.

Experience at a nickel carbonyl refinery has shown that the clinical severity of the acute nickel carbonyl exposure can also be correlated to nickel levels in early urinary samples (within the first 12 hours of exposure). The use of an 8-hour post exposure urinary nickel specimen may also be helpful in categorizing cases and determining the need for chelation therapy.

1.6 Assessing the Risks of Workers Exposed to Nickel

Any efforts to evaluate occupational health risks such as those identified above must start with good data collection. This includes not only monitoring workplace exposures (discussed in greater detail in the next section), but assessing the health of individual workers with the ultimate goal of keeping the worker healthy and reducing the overall risks in the work environment. It is not enough to periodically monitor workers, but programs must be implemented in ways that allow for the systematic collection of data that can be used in epidemiological studies and, subsequently, risk assessment. In some countries, implementation of a health surveillance program is obligatory. In such instances, any company-based surveillance program should be in compliance with the relevant local/national guidelines. Developing infrastructure and systems that support consistent data collection and storage requires effort, careful planning, and an adequate allocation of resources.

The general steps involved in the assessment of risks include:

- Determining the population at risk.
- Identifying the hazards.
- Assessing exposures and health outcomes.
- Developing data collection and management systems.
- Training and benchmarking.

For purposes of risk assessment, records should be kept on most, if not all, workers employed in the nickel industry. This includes not only production workers, but office workers and support staff as well. Consideration should also be given to contractors, such as temporary workers or long-term maintenance crews employed at factories, as some of these workers may be employed in potentially high exposure jobs. Companies should assign a unique identifier to each individual.

It is also important to identify all potentially harmful substances in a workplace and to monitor and control exposures in order to manage the risk. All the nickel species present in an industrial setting should be identified, and a complete inventory of raw materials used, materials produced, by-products, and contaminants should be taken. Consideration should be given to monitoring these materials not only under normal operations, but also when short-term peak exposures occur (*e.g.,* during maintenance). In addition, a record should be made of

all procedures and equipment used (including control equipment such as local exhaust ventilation and respirators), changes in processes, and changes in feed materials. Complementing this description of the worksite should be a description of each worker's employment history, both past and current.

With respect to exposures, two types of exposure data are required: those that pertain to the ambient environment (*e.g.,* workplace air) and those that pertain to the internal environment of the worker (*e.g.,* health surveillance). To be of use in risk assessment, each must be linked to the other. Health surveillance may be used to evaluate an individual's health prior to, during, and at termination of employment. Occasionally, it also may be used during retirement. Considerable clinical skill and judgment are required to assess work-related health effects. Consultation with properly trained personnel is critical. Issues such as the invasiveness, sensitivity, and accuracy of testing procedures must be considered carefully, as should the rights of the workers. Laws regarding discriminatory practices in hiring and job placement should be strictly followed, as should laws regarding recordkeeping. Any health data gathered and recorded should be subject to rigorous quality control.

In structuring a health surveillance program, consideration ideally should be given to the following components:

- Pre-placement assessment. Of particular importance is the identification of pre-existing medical conditions in target organs (notably the respiratory system and skin, but also reproductive and renal systems) that potentially might be affected by nickel and its compounds. A pre-placement assessment should typically include, but not necessarily be limited to: baseline health data, a detailed history of previous disease and occupational exposures, present or past history of allergies (particularly nickel-related) including asthma, identification of personal habits (most notably, smoking) and hobbies, a physical examination (which may include chest X-rays and other pulmonary tests), and evaluation of the ability of a worker to wear respiratory protection equipment.

- Periodic assessment. Such an assessment generally consists of an update of the above, but may also include more extensive testing. Unless mandated more frequently by law, measurements of respiratory function and chest X-rays should be considered around every 5 years. Depending on the age, the smoking status, and the job task (nature and level of exposure), more frequent chest X-rays may be appropriate.

Skin patch testing is not recommended as a routine pre-employment procedure because there is a possibility that such test may sensitize the applicant. However, in special circumstances, such testing may be warranted for purposes of clinical diagnosis. Patch testing should only be undertaken by persons experienced in the use of the technique.

In many industrial health surveillance programs, workers may be monitored for markers of exposure in body fluids, with the intent of establishing a correlation between external exposure, internal exposure (as measured by the marker), and effect. However, in the case of nickel, a biological monitoring program should be implemented only after careful consideration of the facts and limitations of such a program. While of some

value as a marker of exposure, nickel in urine, blood, and other tissues or fluids (with the exception of nickel carbonyl) has not been shown to be predictive of health risks. Given that biological monitoring reflects only the amount of solubilized nickel present in biological materials and not true body burden, its utility is questionable as an early warning device of potential health effects that are generally organ-specific, long-term, and accumulative in nature.

If implemented, a biological monitoring program should augment both environmental monitoring and industrial hygiene programs. It should never be implemented as a "stand alone" program. Given the above limitations, biological monitoring may have a place, but mainly in specific situations, *e.g.,* where exposures are to soluble nickel compounds, fine nickel metal powders, or nickel carbonyl. It is less useful in situations where exposures are predominantly to insoluble compounds of larger particle size or where exposures are mixed. If biological monitoring is undertaken, urinary sampling is generally preferred over serum sampling because it is less invasive and easier to conduct.

It is preferable that any health surveillance program implemented be administered by qualified occupational health specialists. However, once a proper data collection system is in place, non-expert staff, with appropriate training, can help to collect some of the data on a day-to-day basis.

Lastly, any surveillance program that is implemented should be evaluated to determime how well it is working. This entails establishing sound database management systems, filling recognized data gaps, and setting goals against which future evaluations can be made.

1.7 Workplace Surveillance

Knowledge of general exposure conditions within the workplace is another element of a good worker protection program. Workplace surveillance entails understanding applicable legislative/regulatory occupational exposure limits and implementing an air monitoring program that allows for the comparison of worker exposures to these limits. It is necessary for the employer to keep abreast of current recommended and mandated exposure limits regarding nickel and its compounds and to ensure that workplace exposures comply with these limits.

Components of an air monitoring program are:

- development of a sampling strategy,
- purchase or rental of sampling equipment and supplies,
- calibration of equipment,
- sample collection,
- sample analysis,
- calculation of exposure concentrations,
- determination of compliance status,
- notification of employees of the results, and
- documentation and recordkeeping.

Specific requirements for each of these components may differ from country to country. Employers should consult the appropriate government agency and/or code for detailed procedures on establishing an air monitoring program. Air monitoring is not an end in itself but should be considered part of an overall program of risk assessment and management. It is necessary to evaluate monitoring results and decide whether any action is required to modify the sampling procedures or working environment.

When monitoring, it is important that the sampling strategy be flexibly designed to account for differences in worker and job variability. This means that different sampling strategies may need to be employed in different areas of a plant. It is also important to note that while either personal or static sampling devices may be used (provided that regional regulations do not stipulate a particular method), personal sampling is best suited to evaluating worker exposure while static sampling is a preferred tool for data collection for engineering controls. In all cases, the employees' support should be sought by explaining the reason for sampling and asking for their participation.

Recently, the search for a more rational, health-related aerosol sampling has resulted in the development of an inhalable sampler at the Institute of Occupational Medicine. This sampler takes into consideration the efficiency of inhalation of the human head and the deposition of particles in the nasopharyngeal, thoracic and alveolar regions of the respiratory tract.

Side-by-side comparisons of the inhalable sampler to "total" aerosol samplers (such as the 37 mm sampler) have shown the inhalable sampler to consistently measure 2-3 times more aerosol than the "total" sampler. The observed biases tended to be greater for workplaces where aerosols are coarser.

As noted above, health effects associated with nickel exposures may be dependent upon a number of factors including chemical form (speciation), particle size, and solubility within biological fluids. Research projects currently underway are designed to provide new methods and means for collecting biologically-meaningful aerosol fractions. In fact, the American Conference of Governmental Industrial Hygienists (ACGIH) set its 1998 Threshold Limit Value (TLV) recommendations for nickel compounds based upon the "inhalable" particulate fraction. Countries that use the ACGIH TLVs to set their own Occupational Exposure Limits will be likely to make the appropriate changes. In the interim, it may be prudent to begin a program of evaluating the use of an inhalable dust fraction sampler, obtain measurements of particle size distribution, and to determine nickel species in samples when reasonably practicable.

Good industrial hygiene practice requires that an employer provide the sampled employees (and those unsampled employees whose exposures they are deemed to represent) with their personal sampling results and an explanation of their meaning. Group results should also be shared with the workforce. Where the results of sampling "representative" individual(s) are made available to other workers, consideration should be given to withholding personal identifiers. Exposure recordkeeping requirements may vary from country to country; hence, it is advisable to consult with the appropriate authority for details on possible mandatory requirements. Like health data, exposure monitoring data should be subject to rigorous quality control.

1.8 Control Measures

Whenever conditions suggest high exposures or monitoring indicates a potential for overexposure, measures to control exposures should be taken. Control options fall into four categories:

- engineering controls,
- administrative controls,
- control through work practices, and
- personal protective equipment (PPE)

Typically, engineering, administrative, and work practice controls are preferred over PPE when feasible. Since regulatory authorities may differ in their definition of "feasible" controls, employers should contact their respective authority for specific guidelines.

Three categories of engineering controls generally are considered – substitution, enclosure, and ventilation. Of these three options, ventilation is probably the most widely employed as a means of controlling exposures, although it is not necessarily the most effective in all situations. In choosing among options, consideration should be given to the nature of the operation (*e.g.,* is the operation likely to be continuously dusty), the materials handled, feasibility, and regulatory requirements.

When employed, exhaust fans and exhaust ventilation (*i.e.,* exhaust hoods at the source of exposure) are preferred over intake fans for work area ventilation. Ventilation design is complex and should be undertaken only by suitably trained engineers. The designer should consider both the regulations that govern exposure to workplace contaminants and the process operation itself, including the materials being used and the frequency with which they are handled.

Administrative controls, such as employee rotations and workshift modification, can also be used to reduce individual exposures, but such practices should be secondary to engineering controls.

In any industrial setting, it is important to engage in good housekeeping and personal hygiene practices. In the nickel industry, special care should also be taken to reduce the risk of contact dermatitis (*e.g.,* by wearing protective clothing and gloves) and the risk of inhaling nickel in excess of permissible limits. Because smoking is the most common cause of respiratory cancer, it should be discouraged, if not banned.

Personal protective equipment (PPE) ordinarily is the last control option considered. Use of PPE should occur under a properly administered program. When the use of respirators is involved, a written program should be established which describes management and employee responsibilities, respirator selection, fitting, and fit-testing, employee instruction and training, medical screening, and program evaluation. Because recommendations on the use of respirators and other protective equipment may vary from country to country, employers should contact their appropriate authority for guidance.

1.9 Limit Values and Hazard Communication

A number of countries and jurisdictions have established specific regulatory requirements for hazard communication relating to the use, handling, and presence of chemicals in the workplace. Such information must be relayed to workers and sometimes to a variety of "end-users" of the chemical, as well as any other parties that may be affected by exposure to the chemical.

Generally speaking, three components comprise a hazard communication program: labeling, Material Safety Data Sheets (MSDS), and worker training. The producer/supplier is responsible for preparing labels and MSDSs and seeing that these are delivered to its customer. Worker training is the responsibility of all employers, regardless of industry sector. As important differences may exist between jurisdictions, employers should contact their relevant authorities for further detailed information on such programs and any specific requirements pertaining to nickel.

2. Production And Use

Apart from unusual sources, such as massive nickel in meteorites, nickel from natural sources is usually found at modest concentrations and occurs in conjunction with a wide variety of other metals and non-metals. Although nickel is a ubiquitous metal in the natural environment, industrialization has resulted in increased concentrations of nickel in both rural and urban environments.

Nickel-bearing particles are present in the atmosphere as constituents of suspended particulate matter and, occasionally, of mist aerosols. The primary anthropogenic stationary source categories that emit nickel into ambient air are: (1) combustion and incineration sources (heavy residual oil and coal burning units in utility, industrial, and residential use sectors, and municipal and sewage sludge incinerators), (2) high temperature metallurgical operations (steel and nickel alloy manufacturing, secondary metals smelting, and co-product nickel recovery), (3) primary production operations (mining, milling, smelting, and refining), and (4) chemical and catalyst sources (nickel chemical manufacturing, electroplating, nickel-cadmium battery manufacturing, and catalyst production, use, and reclamation). Typical ambient air concentrations of nickel range from 0.03 (North Sea remote site) to 21 ng Ni/m^3 (industrially influenced site) (Working Group on As, Cd and Ni Compounds, 2001).

In aquatic systems, such as in ambient or drinking water, nickel is usually present as the nickel cation (Ni^{2+}), together with other anions such as hydroxyl (OH^-), sulfate (SO_4^{2-}), chloride (Cl^-), carbonate (CO_3^{2-}), or nitrate (NO_3^-). Sources of nickel in ambient waters include chemical and physical degradation of rocks and soils, deposition of atmospheric nickel-containing particulate matter, and discharges from industrial processes. The recently completed EU Risk Assessment of Nickel reported ambient dissolved nickel concentrations for typical European freshwater systems ranging from 1 to 6 µg Ni/L. Higher and lower concentrations may be encountered in waters with specific geological influences, but nickel concentrations for most freshwater systems will fall within this general range. Nickel levels in soil vary between 5 and 500 µg Ni/g depending on geological factors.

For purposes of this document, however, the main concern is nickel presence in occupational settings. The use of nickel, although concentrated in the traditional uses of stainless steels and high-nickel alloys, continues to find new uses based on magnetic, catalytic, shape-memory, electro-magnetic shielding, electrical, and other esoteric properties. Thus more nickel in small quantities and in various forms will be used in more industries and applications. The contributions being made by nickel have never been greater but neither has the need for an understanding of nickel.

It is evident that industrial processes present potential for exposure of workers to higher concentrations of nickel and/or its compounds than those generally found in the natural environment. Occasionally, these exposures may be to a refined form of nickel, but usually they are mixed, containing several nickel compounds and/or contaminants. These “mixed exposures” often complicate the interpretation of health effects of specific nickel species.

2. Production And Use

2.1 Nickel-producing Industries

Workers engaged in nickel production–which may include mining, milling, concentrating, smelting, converting, hydrometallurgical processes, refining, and other operations–are exposed to a variety of nickel minerals and compounds depending upon the type of ore mined and the process used to produce intermediate and primary nickel products (Nickel Institute, 2008). These production processes are often broadly grouped under the industry sectors of mining, milling, smelting, and refining.

Generally, exposures in the producing industry are to moderately soluble and insoluble forms of ores and nickel, such as pentlandite $(Ni,Fe)_9S_8$, nickeliferous pyrrhotite, $(Fe,Ni)_{1-x}S$, nickel subsulfide (Ni_3S_2), silicates (including garnierite and smelting slags), and oxidic nickel (including nickeliferous limonite, NiO, Ni-Cu oxides, and complex oxides with other metals such as iron and cobalt). Exposures to metallic and soluble nickel compounds are less common. Soluble nickel compounds are more likely to be found in hydrometallurgical operations, such as leaching and electrowinning, than in mining and smelting operations (Nickel Institute, 2008).

Primary nickel products produced from the above operations are often characterized as Class I and II. Class I products are pure nickel metal, defined as containing ≥99.8% Ni (Table 1). Class II products have <99.8% Ni and encompass three different types of products: metallic nickel in various product forms, nickel oxides, and ferronickels (Table 2).

Class I products are marketed in a variety of forms including pure electrolytic full-plates, nickel squares, rounds, or crowns, spherical pellets, briquettes of consolidated pure nickel powder compacts, and pure nickel powders. The metallic nickels in Class II are electrolytic nickel products and briquettes containing >99.7% Ni, but <99.8% Ni and utility nickel shot containing >98.7% Ni. The oxide products in Class II include rondelles–partially reduced nickel oxide compacts containing about 90% Ni–and compacts of nickel oxide sinter containing approximately 75% Ni. The ferronickel products contain about 20% to 50% Ni.

Table 2-1: Class I Primary Nickel Products, 99.8 Percent Nickel or More

Product Name	Nickel Content, Wt%	Form	Principal Impurity
Electro – electrolytic nickel squares, rounds, crowns	99.8 - 99.99	Massive	Various
Pellets – from nickel carbonyl	>99.97	Massive	Carbon
Briquettes – metallized powder compacts	≥99.8	Massive (possibility of some powder formation during transport and handling)	Cobalt
Powders – by carbonyl decomposition or by precipitation	≥99.8	Dispersible	Carbon

2. Production And Use

Table 2-2: Class II Primary Nickel Products, Less than 99.8 Percent Nickel			
Product Name	**Nickel Content, Wt%**	**Form**	**Principal Impurity**
Electro	>99.7	Massive	Cobalt
Briquettes	>99.7	Massive (possibility of some powder formation during transport and handling)	Cobalt
Utility – shot	>98.7	Massive	Iron
Sinter – nickel oxide and partially metallized	~75 - 90	Massive (possibility of some powder formation during transport and handling)	Oxygen
Ferronickel – ingots, cones, shot, granules	~20 - 50	Massive	Iron

While the processes of each of these producers differ, they may be broadly classified into two groups: (1) those in which nickel is recovered from sulfidic ores (generally, but not always, found in the temperate zones of the earth's crust) and (2) those which are recovered from lateritic ores (commonly present in areas that currently are, or geologically were, tropical and semi-tropical areas). Traditionally the sulfidic ores have dominated but that is shifting and future primary nickel production will be more dependent on lateritic ores. It is important to note, however, that secondary sources of nickel – overwhelmingly in the form of scrap stainless steels and nickel alloys but also including spend catalysts, batteries and other products – will constitute a large and ever increasing percentage of world nickel supply.

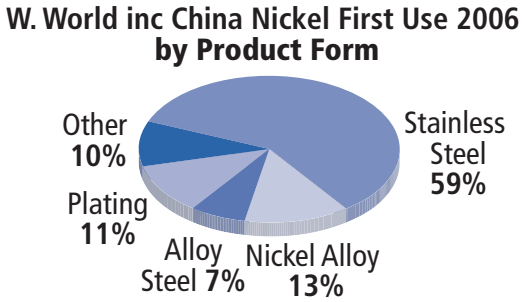
With the exception of inhalable nickel powders, all the above products are massive and cannot be inhaled. However, in some instances, inhalable particles may be generated as a result of the degradation of briquettes, rondelles, and sinters during production, handling, packaging, shipping, unpacking, or subsequent treating or processing of these products.

The primary nickel industry is growing and evolving. There are a number of new entrants and a number of established producers are now part of some of the largest mining companies in the world. Smelting or refining operations take place in more than a dozen countries and are fed with concentrates from many more. The volumes in domestic and international trade are increasing, as are the ways in which the intermediate and finished products are packaged and transported.

2.2 Nickel-using Industries

Various public and private statistical services track the production and end-use of nickel. The divisions vary and all percentages are "best estimates" but the 2006 numbers given below provide reasonable breakdowns.

Figure 1



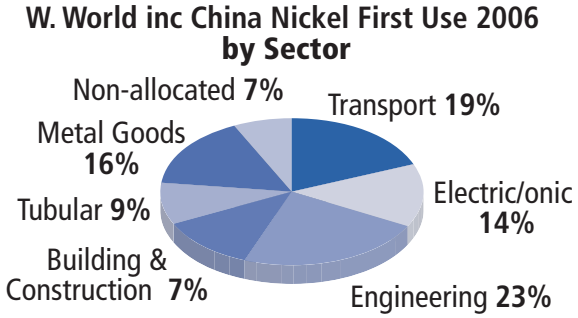
2. Production And Use

Figure 1 (Pariser, 2007) shows nickel use by industry sector. It indicates that almost 80 percent of all nickel is used in the production of different stainless and alloy steels, other nickel alloys (of which there are thousands) and foundry products. About eleven percent is used in plated products, and the remaining ten percent goes into catalysts, battery chemistries of various types, coinage, pigments and literally thousands of other small chemical uses.
There is a constant stream of new uses for nickel where small uses of nickel are providing gains in environmental (including energy efficiency and carbon emission) performance.

Most of the plating and "other" applications are "end-uses" of nickel; that is to say, the products are used directly by the customer or "end-user."

The steels and other nickel alloys, on the other hand, are "intermediate" products that must be further processed or "transformed" into end-use commercial products in a number of industrial applications. These applications include building and construction materials; tubes; metal goods; transportation, electrical and electronic; engineering; and consumer and other products (Figure 2) (Pariser, 2007).

Figure 2



Only the most superficial description of nickel production and use are given here and only to provide context for the occupational health management issues that are the focus of this publication. For more information on nickel production and use, including end-of-life management, of nickel and nickel-containing materials and products, contact the Nickel Institute at: www.nickelinstitute.org.

3. Sources Of Exposure

Given its many uses and applications, the potential for exposure to nickel, its compounds, and alloys is varied and wide ranging. Of main concern to this document are occupational exposures. Non-occupational exposures are briefly mentioned at the end of this section.

3.1 Occupational Exposures

Although exposure to specific forms of nickel differs among using and producing industries, the main exposure routes of toxicological relevance – inhalation and, to a lesser extent, skin contact – are the same in both industries.

The wide range of occupations with direct exposure to nickel via these routes of exposure are summarized below within 13 different industrial sectors. These sectors are:

- refining, main part of the refining processes;
- last stage refining, handling of primary nickel;
- alloy production, melting and foundry techniques;
- alloy production, powder metallurgy;
- batteries, nickel metal as feedstock;
- batteries, unknown type of nickel species as feedstock;
- nickel catalysts, nickel metal as feedstock;
- nickel catalyst, unknown type of nickel species as feedstock;
- nickel in the production of chemicals;
- contact with coins;
- contact with tools and other nickel releasing surfaces;
- use of batteries; and
- use of catalysts.

The first two sectors correspond to the nickel-producing industry, while the rest belong to the nickel-using industry.

Current exposures for all the industry sectors noted above are summarized in Table 3-1. Current data–generally acquired over the past 10 to 20 years, but occasionally representing data recorded since the late 1970s–typically represent actual measurements derived from standard procedures of 'total' aerosol sampling (*e.g.*, through methods developed by the UK's Health and Safety Executive or the US' National Institute of Occupational Safety and Health). The data for this table come from a variety of sources including:

- published, peer-reviewed literature,
- company or agency reports in general circulation,
- company or agency internal reports not in general circulation but accessible through those organizations,
- company or agency databases and log-books obtainable through direct personal contacts, and
- follow-up through direct personal contacts (where appropriate and feasible) to fill gaps in information relevant to the evaluation.

From this table, it can be seen that exposures in the nickel-producing sectors have generally been reduced over time so that they now tend to be lower than in the using sectors, although there are some exceptions. For example, average exposures in primary nickel refining tend to be relatively low (around 0.07 mg Ni/m^3), whereas average exposures in chemical blending and nickel catalyst production average 0.3-0.5 mg Ni/m^3.

3. Sources Of Exposure

It is also clear from Table 3-1 and the footnotes to this table that the range of exposures in any given industry sector can vary widely. Workers employed in some jobs and activities in a sector with generally low exposures could well be exposed for days, weeks, or even years to levels of nickel aerosols well above those of some workers employed in another sector which experiences generally high exposures. Thus, it is unwise to regard occupational exposures within sectors as uniform among jobs, among workers within jobs, or within workers from day to day, without gathering further data on the particular industry sector of concern.

While it is clear that certain forms of nickel tend to predominate in different industry sectors (*e.g.*, soluble nickel in plating), it appears that in no industry sector are workers exposed purely to one form of nickel. Hence, an understanding of the health effects of individual nickel species cannot be obtained from human data alone. Animal and human data, in conjunction with mechanistic studies, need to be considered as part of the weight-of-evidence required for determining species-specific occupational exposure limits. In addition, although little is currently known about the effects of particle size relative to speciation, it should be borne in mind that the size of the nickel particles to which workers are exposed is likely to play an important role in the biological effects of different nickel species. To the extent that such data are available, they are discussed in this document.

3.2 Non-occupational Exposures

Nickel is ubiquitous and can be found in ambient air, water, food, and soil. Some of this nickel is naturally occurring; however, some is introduced into the environment as a result of human activity. Human exposure to nickel can also occur through skin contact with nickel-containing articles, such as jewelry, through nickel-containing implants, through the leaching of nickel into dialysate fluids, and through tobacco smoke.

3. Sources Of Exposure

Table 3-1: Estimated Inhalation and Dermal Exposure to Nickel Species in Nickel-Producing and -Using Industries

Industry Sector	Time scale of exposure		Estimated exposure to inhalable nickel (mg/m^3)									Dermal exposure (mg/day)			
	Duration (hr/day)	Frequency (day/year)	Full shift (8 hour time weighted average)						Short-term			Typical		Worst-case	
			Typical level		Method	Worst-case level		Method	Level		Method				
Refining, main part of the refining processes	6-8	200	0.004 0.0064 0.003 0.065	M[1] SO SU O	Meas.[3]	1.1 0.33 0.55 9	M SO SU O	Meas.	2.2 0.65 1.1 18	M SO SU O	Exp.[4]	0.4[3] 0.6[3]	U SO	2.0[3] 1.8[3]	U SO
Last stage Refining, handling of primary nickel	6-8	200	0.06 0.006	M SO	Meas.	6.0	M	Meas.	12	M	Exp.	13[3] 5.1[3]	U SO	22[3] 8.7[3]	U SO
Alloy production, melting and foundry techniques	6-8	200	0.012 0.0012 ~0 0.045	M SO SU O	Meas.	7 0.28 ~0 7	M SO SU O	Meas.	14 0.6 ~0 14	M SO SU O	Exp.	1.8[6] 0.4[6]	U SO	16[6] 1.8[6]	U SO
Alloy production, powder metallurgy; the powder was considered to be all metallic nickel	6-8	200	0.5	M	Meas.	2.1	M	Meas.	4.2	M	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Batteries, nickel metal as feedstock	6-8	200	0.3	M	Meas.	2.7	M	Meas.	5.4	M	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Batteries, unknown type of nickel species as feedstock	6-8	200	0.02	T	Meas.	0.3	T	Meas.	0.6	T	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Nickel catalysts, nickel metal as feedstock	6-8	200	0.06[5]	M	Meas.	5.0[5]	M	Meas.	10[5]	M	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Nickel catalyst, unknown type of nickel species as feedstock	6-8	200	0.09[5]	T2	Meas.	1.2[5]	T[2]	Meas.	2.4[5]	T[2]	Meas.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Nickel in the production of chemicals	6-8	200	0.006- 0.45[9]	T	Meas.	7.0[5]	T	Meas.	14[5]	T	Exp.	13[7] 5.1[7]	U SO	22[7] 8.7[7]	U SO
Contact with coins	6-8	200	0.001	M	Meas.	0.018	M	Meas.	0.036	M	Exp.	0.04[8]	M	0.12[8]	M
Contact with tools and other nickel releasing surfaces	6-8	200	~0	M	Exp.	~0	M	Exp.	~0	M	Exp.	0.04[8]	M	0.12[8]	M
Use of batteries	6-8	200	~0	M	Exp.	~0	M	Exp.	~0	M	Exp.	~0	M	~0	M
Use of catalysts	6-8	200	~0	M	Exp.	~0	M	Exp.	~0	M	Exp.	~0	M	~0	M

1: M = Metallic nickel; O = Oxidic nickel; SO = Soluble nickel; SU = Sulphidic nickel; T = The predominant nickel species include metallic nickel, oxidic nickel, and soluble nickel salts; U = Other nickel species than soluble nickel. 2: Exposure to sulphidic nickel cannot be excluded. 3: The estimate was derived from measured data. 4: 'Expert judgement'. 5: The values may be overestimates. 6: The mass of material deposited on the skin was estimated by analogy to dermal exposure measured for cathode cutting and briquette packing operators 7: Estimated by analogy to measured data for nickel powder packing operators. 8: The estimate is for both hands (surface area 840 cm2). 9: Range of estimated typical exposure levels.

3. Sources Of Exposure

3.3 Nickel Emissions

Determination of the potential for nickel exposure depends to a large degree on the reliability of analytical data from environmental samples and biological specimens. This is particularly true when trying to differentiate between anthropogenic and natural contributions of nickel to environmental samples. Concentrations of nickel in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. Attention must also be paid to the fact that the amount of nickel identified through analytical techniques is not necessarily equivalent to the amount that is bioavailable (*i.e.,* available for absorption into the body).

Emissions to the atmosphere from the industrial production and use of nickel are approximately 14.5 x 10^6 kg/year. At the same time, natural emissions from volcanism, dust storms, fires, *etc.* contribute approximately 8.5 x 10^6 kg/year. However, natural and industrial emissions combined are substantially less than the emissions from fuel combustion which total approximately 28.6 x 10^6 kg/year. Eisler (1998) quotes a figure of 16% of the atmospheric nickel burden due to natural sources, and 84% due to anthropogenic sources, which agrees with these figures.

The figure given for emissions of nickel to the atmosphere due to intentional production and use of nickel is approximately 13 x 10^6 kg Ni/y. There are larger differences in the estimates for the contribution from other anthropogenic sources. These range from 28.6 x 10^6 kg Ni/y (Bennett, 1984) to a total of 43.4 . 10^6 kg/year (Niagu, 1989). This difference is however very small compared to the range of estimates for emissions from natural sources which range from 8.5 x 10^6 kg/year (Bennett, 1984) to 1800 x 10^6 kg/year (Richardson *et al.*, 2001). The uncertainties in the estimates of nickel emissions from processes not related to intentional nickel production suggest that the relative contribution of nickel emissions associated with intentional nickel production and use may have been overestimated in earlier reviews.

Chemical and physical degradation of rocks and soils, atmospheric deposition of nickel-containing particulates, and discharges of industrial and municipal waste release nickel into ambient waters (US EPA, 1986). The main anthropogenic sources of nickel in water are primary nickel production, metallurgical processes, combustion and incineration of fossil fuels, and chemical and catalyst production (US EPA, 1986). These are the same sources that contribute to emissions to the atmosphere.

The primary anthropogenic source of nickel to soils is disposal of sewage sludge or application of sludge as a fertilizer. Secondary sources include industrial nickel production and use, and emissions from electric power utilities and automobiles. Weathering and erosion of geological materials also release nickel into soils (Eisler, 1998).

4. Pharmacokinetics Of Nickel Compounds

Factors of biological importance to nickel, its compounds, and alloys include solubility, chemical form (species), physical form (*e.g.*, massive versus dispersible), particle size, surface area, concentration, and route and duration of exposure. Where possible, the relationship of these factors to the intake, absorption, distribution, and elimination of nickel is discussed in this section. Independent factors that can also affect the biokinetic activity of nickel species, such as disease states and physiological stresses, are briefly noted.

4.1 Intake

The major routes of nickel intake are dietary ingestion and inhalation. In most individuals, even some who are occupationally exposed, diet constitutes the main source of nickel intake. The average daily dietary nickel intake for U.S. diets is 69-162 µg Ni/day (NAS 2002; O'Rourke *et al.*, 1999; Pennington and Jones 1987; Thomas *et al.*, 1999). These values agree with those from European studies. However, consumption of foodstuffs naturally high in nickel, such as oatmeal, cocoa, chocolate, nuts, and soy products, may result in higher nickel intake (Nielsen and Flyvolm, 1984; Grandjean *et al.*, 1989).

Nickel in potable water also is generally quite low, averaging from <0.001 to <0.010 mg Ni/L (Grandjean *et al.*, 1989). Assuming an intake of 2 L/day, either as drinking water or water used in beverages, nickel in water may add 0.002 to 0.02 mg Ni to total daily intake.

For individuals who are not occupationally exposed to nickel, nickel intake *via* inhalation is considerably less than dietary intake. The Ni concentration of particulate matter in the atmosphere of the United States ranges from 0.01 to 60, 0.6 to 78, and 1 to 328 ng/m^3 in remote, rural, and urban areas, respectively (Schroeder *et al.*, 1987). Average ambient air Ni concentrations in U.S. and Canadian cities range from 5 to 50 ng/m^3 and 1 to 20 ng/m^3, respectively. Nickel concentrations in indoor air are typically <10 ng/m^3 (Graney *et al.*, 2004; Kinney *et al.*, 2002; Koutrakis *et al.*, 1992; Van Winkle and Scheff 2001).

Higher nickel air values have been recorded in heavily industrialized areas and larger cities (IPCS, 1991). An average urban dweller (70 kg man breathing 20 m^3 of 20 ng Ni/m^3/day) would inhale around 0.4 µg Ni/day (Bennett, 1984). For rural dwellers, daily intake of airborne nickel would be even lower.

Ultimately, the general population absorbs the greatest amount of nickel through food. Typical daily intakes of nickel from drinking water and inhalation of air are approximately 20 µg and 0.4 µg, respectively.

For occupationally exposed individuals, total nickel intake is likely to be higher than it is for the general populace. Whether diet or workplace exposures constitute the main source of nickel intake in workers depends upon a number of factors. These factors include the aerodynamic size of the particle and whether it is inhalable, the concentration of the nickel that is inhaled, the minute ventilation rate of a worker, whether breathing is nasal or oronasal, the use of respiratory protection equipment, personal hygiene practices, and general work patterns.

Based upon the exposure estimates presented in Section 3 and assuming that a total of 12 m^3 of air is inhaled in an eight-hour work day (the as-

sumption being that industrial workers have a higher inhalation rate than the average citizen), the approximate amount of nickel likely to be inhaled in nickel-producing industries would range from 0.036 to 0.72 mg Ni/day. The average amount of nickel likely to be inhaled in most nickel-using industries would range from ~0 to 1.1 mg Ni/day depending upon the industry. Battery production with metallic nickel and metallic nickel powder metallurgy operations are an exception, with average airborne nickel concentrations (based on reports that have been made occasionally) ranging from 0.3 to 0.5 mg Ni/m^3, respectively.

Other sources of exposure include contact with nickel-containing items (*e.g.,* jewelry), medical applications (*e.g.*, prostheses), and tobacco smoke. Dermal exposure to nickel-containing articles constitutes one of the most important routes of exposure for the public with respect to allergic contact dermatitis. Likewise, tobacco smoking may also be a source of nickel exposure. Some researchers have suggested that smoking a pack of 20 cigarettes a day may contribute up to 0.004 mg Ni/day (Grandjean, 1984). While this would contribute little to total nickel intake, smoking cigarettes with nickel-contaminated hands can significantly increase the potential for oral nickel exposures.

4.2 Absorption

4.2.1 Respiratory Tract Deposition, Absorption and Retention

Toxicologically speaking, inhalation is the most important route of nickel exposure in the workplace, followed by dermal exposure. Deposition, absorption, and retention of nickel particles in the respiratory tract follow general principles of lung dynamics. Hence, factors such as the aerodynamic size of a particle and ventilation rate will largely dictate the deposition of nickel particles into the nasopharyngeal, tracheobronchial, or pulmonary (alveolar) regions of the respiratory tract.

Not all particles are inhalable. As noted in Section 2, many primary nickel products are massive in form and hence inherently not inhalable. However, even products which are "dispersible" may not necessarily be inhalable unless the particles are sufficiently small to enter the respiratory tract. Humans inhale only about half of the particles with aerodynamic diameters >30 µm, and it is believed that this efficiency may decline rapidly for particles with aerodynamic diameters between 100 and 200 µm. Of the particles inhaled, only a small portion with aerodynamic diameters larger than 10 µm are deposited in the lower regions of the lung, with deposition in this region predominantly limited to particles ≤4 µm (Vincent, 1989).

Factors such as the amount deposited and particle solubility, surface area, and size will influence the behavior of particles once deposited in the respiratory tract and will probably account for differences in retention and clearance *via* absorption or through mechanical means (such as mucociliary clearance). Physiological factors such as age and general health status may also influence the process. Unfortunately, little is known about the precise pharmacokinetics of nickel particles in the human lung.

Based largely upon experimental data, it can be concluded that the more soluble the compound, the more readily it is absorbed from

4. Pharmacokinetics Of Nickel Compounds

the lung into the bloodstream and excreted in the urine. Hence, nickel salts, such as sulfate and chloride, are rapidly absorbed and eliminated. The half-life of nickel in the lungs of rats exposed by inhalation has been reported to be 32 hours for nickel sulfate (mass median aerodynamic diameter [MMAD] 0.6 µm) (Hirano *et al.* 1994), 4.6 days for nickel subsulfide ($^{63}Ni_3S_2$ activity median aerodynamic diameter [AMAD] 1.3 µm), and 120 days for green nickel oxide (^{63}NiO, AMAD 1.3 µm) (Benson *et al.*, 1994). Elimination half-times from the lung of rats of 7.7, 11.5, and 21 months were calculated for green nickel oxide with MMADs of 0.6, 1.2, and 4.0 µm, respectively (Tanaka *et al.*, 1985, 1988).

The relatively insoluble compounds, such as nickel oxides, are believed to be slowly absorbed from the lung into the bloodstream, thus, resulting in accumulation in the lung over time (see Section 6.3). Dunnick *et al.* (1989) found that equilibrium levels of nickel in the lungs of rodents were reached by 13 weeks of exposure to soluble $NiSO_4$ (as $NiSO_4 \bullet 6H_2O$) and moderately soluble Ni_3S_2, but levels continued to increase with exposure to NiO. There is also evidence that some of the nickel retained in lungs may be bound to macromolecules (Benson *et al.*, 1989).

In workers presumably exposed to insoluble nickel compounds, the biological half-time of stored nickel in nasal mucosa has been estimated to be several years (Torjussen and Andersen, 1979). Some researchers believe that it is the accumulated, slowly absorbed fraction of nickel which may be critical in producing the toxic effects of nickel *via* inhalation. This is discussed in Section 5 of this Guide.

Workers occupationally exposed to nickel have higher lung burdens of nickel than the general population. Dry weight nickel content of the lungs at autopsy was 330±380 µg/g in roasting and smelting workers exposed to less-soluble compounds, 34±48 µg/g in electrolysis workers exposed to soluble nickel compounds, and 0.76±0.39 µg/g in unexposed controls (Andersen and Svenes 1989). In an update of this study, Svenes and Andersen (1998) examined 10 lung samples taken from different regions of the lungs of 15 deceased nickel refinery workers; the mean nickel concentration was 50 µg/g dry weight. Nickel levels in the lungs of cancer victims did not differ from those of other nickel workers (Kollmeier *et al.*, 1987; Raithel *et al.*, 1989). Nickel levels in the nasal mucosa are higher in workers exposed to less soluble nickel compounds relative to soluble nickel compounds (Torjussen and Andersen 1979). These results indicate that, following inhalation exposure, less-soluble nickel compounds remain deposited in the nasal mucosa.

Acute toxicokinetic studies of NiO or $NiSO_4 \bullet 6H_2O$ in rodents and monkeys and subchronic repeated inhalation studies in rodents have been conducted to determine the effects of nickel compounds on lung clearance (Benson *et al.*, 1995). Clearance of NiO from lungs was slow in all species. Impairment of clearance of subsequently inhaled radiolabled NiO was seen in rodents, particularly at the highest concentrations tested (2.5 mg NiO/m^3 in rats and 5.0 mg NiO/m^3 in mice). In contrast to the NiO-exposed animals, clearance of $NiSO_4 \bullet 6H_2O$ was rapid in all species, and no impaired clearance of subsequently inhaled radiolabeled $NiSO_4 \bullet 6H_2O$ was observed.

Measurements of deposition, retention, and clearance of nickel compounds are lacking in humans.

4.2.2 Dermal Absorption

Divalent nickel has been shown to penetrate the skin fastest at sweat ducts and hair follicles where it binds to keratin and accumulates in the epidermis. However, the surface area of these ducts and follicles is small; hence, penetration through the skin is primarily determined by the rate at which nickel is able to diffuse through the horny layer of the epidermis (Grandjean *et al.*, 1989). Nickel penetration of skin is enhanced by many factors including sweat, solvents, detergents, and occlusion, such as wearing gloves (Malten, 1981; Fischer, 1989; Wilkinson and Wilkinson, 1989).

Although dermal exposure to nickel-containing products constitutes an important route of exposure for the public, the amount of nickel absorbed from such products is unknown. In a study using excised human skin, only 0.23 percent of an applied dose of nickel chloride permeated non-occluded skin after 144 hours, whereas 3.5 percent permeated occluded skin in the same period (*i.e.,* skin with an airtight seal over the test material on the epidermal side). Nickel ions from a chloride solution passed through the skin approximately 50 times faster than nickel ions from a sulfate solution (Fullerton *et al.*, 1986).

4.2.3 Gastrointestinal Absorption

Gastrointestinal absorption of nickel is relevant to workplace safety and health insofar as the consumption of food or the smoking of cigarettes in the workplace or without adequate hand washing can result in the ingestion of appreciable amounts of nickel compounds.

Intestinal absorption of ingested nickel varies with the type of food being ingested and the type and amount of food present in the stomach at the time of ingestion (Solomons *et al.*, 1982; Foulkes and McMullen, 1986). In a human study where a stable nickel isotope (^{63}Ni) was administered to volunteers, it was estimated that 29-40% of the ingested label was absorbed (based on fecal excretion data) (Patriarca *et al.*, 1997).
Serum nickel levels peaked 1.5 and 3 hours after ingestion of nickel (Christensen and Lagesson 1981; Patriarca *et al.*, 1997; Sunderman *et al.*, 1989). In workers who accidentally ingested water contaminated with nickel sulfate and nickel chloride, the mean serum half-time of nickel was 60 hours (Sunderman *et al.*, 1988). This half-time decreased substantially (27 hours) when the workers were treated intravenously with fluids.

Other human absorption studies show that 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given in the drinking water (27±17%) than when it was given in food (0.7±0.4%) (Sunderman *et al.*, 1989). The rate constants for absorption, transfer, and elimination did not differ significantly between nickel ingested in drinking water and food. The bio-availability of nickel as measured by serum nickel levels was elevated in fasted subjects given nickel sulfate in drinking water (peak level of 80 µg/L after 3 hours) but not when nickel was given with food (Solomons *et al.*, 1982).

Studies in rats and dogs indicate that 1-10% of nickel, given as nickel, nickel sulfate, or nickel chloride in the diet or by gavage, is rapidly absorbed by the gastrointestinal tract (Ambrose *et*

al., 1976; Ho and Furst 1973; Tedeschi and Sunderman, 1957). In a study in which rats were treated with a single gavage dose of a nickel compound (10 nickel) in a 5% starch saline solution, the absorption could be directly correlated with the solubility of the compound (Ishimatsu *et al.*, 1995). The percentages of the dose absorbed were 0.01% for green nickel oxide, 0.09% for metallic nickel, 0.04% for black nickel oxide, 0.47% for nickel subsulfide, 11.12% for nickel sulfate, 9.8% for nickel chloride, and 33.8% for nickel nitrate. Absorption was higher for the more soluble nickel compounds.

Clearly, good industrial hygiene practices should include the banning of food consumption and cigarette smoking in areas where nickel compounds are used and should include requirements for hand washing upon leaving these areas.

4.3 Distribution

The kinetic processes that govern transport and distribution of nickel in the body are dependent on the site of absorption, rate and concentration of nickel exposure, solubility of the nickel compound, and physiological status of the body. Nickel is mainly transported in the blood through binding with serum albumin and, to a lesser degree, histidine. The nickel ion may also bind with body proteins to form a nickel-rich metalloprotein (Sunderman *et al.*, 1986).

Postmortem analysis of tissues from ten individuals who, with one exception, had no known occupational exposure to nickel, showed highest nickel concentrations in the lungs, thyroid gland, and adrenal gland, followed by lesser concentrations in the kidneys, heart, liver, brain, spleen and pancreas (Rezuke *et al.*, 1987). These values are in general agreement with other autopsy studies that have shown highest concentrations of nickel in lung, followed by lower concentrations in kidneys, liver, heart, and spleen (Nomoto, 1974; Zober *et al.*, 1984a; Seemann *et al.*, 1985).

The distribution of various nickel compounds to tissues has been studied in animals. Such studies reveal that the route of exposure can alter the relative amounts of nickel deposited in various tissues. Animal studies indicate that inhaled nickel is deposited primarily in the lung and that lung levels of nickel are greatest following inhalation of relatively insoluble NiO, followed by moderately soluble Ni_3S_2 and soluble $NiSO_4$ (as $NiSO_4 \cdot 6H_2O$) (Dunnick *et al.*, 1989). Following intratracheal administration of Ni_3S_2 and $NiSO_4$, concentrations of nickel were found to be highest in the lung, followed by the trachea, larynx, kidney, and urinary bladder (Valentine and Fisher, 1984; Medinsky *et al.*, 1987). Kidney nickel concentrations have been shown to increase in proportion to exposure to $NiSO_4$ *via* inhalation, indicating that a significant portion of soluble nickel leaving the respiratory tract is distributed to the kidneys (Benson *et al.*, 1988). There is also some evidence that the saturation of nickel binding sites in the lung or saturation or disruption of kidney reabsorption mechanisms in rats administered $NiSO_4$ results in more rapid clearance (Medinsky *et al.*, 1987).

Not surprisingly, predictions of body burden have varied depending upon the analytical methods used and the assumptions made by investigators to calculate burden. Bennett (1984) estimates the average human nickel body burden to be about 0.5 mg (0.0074 mg/kg x 70 kg). In contrast, values of 5.7 mg have been estimated

by Sumino *et al.* (1975) on the basis of tissue analyses from autopsy cases.

4.4 Excretion

Once absorbed into the blood, nickel is predominantly extracted by the kidneys and excreted in urine. Urinary excretion of nickel is thought to follow a first-order kinetic reaction (Christensen and Lagesson, 1981).

Urinary half-times in workers exposed to nickel *via* inhalation have been reported to vary from 17 to 39 hours in nickel platers who were largely exposed to soluble nickel (Tossavainen *et al.*, 1980).

Relatively short urinary half-times of 30 to 53 hours have also been reported in glass workers and welders exposed to relatively insoluble nickel (Raithel *et al.*, 1982; cited in IARC, 1990; Zober *et al.*, 1984). It should be noted, however, that in these cases the insoluble nickel that workers were exposed to – probably NiO or complex oxides – was likely in the form of welding fumes or fine particles (Zober *et al.*, 1984; Raithel *et al.*, 1981). Such particles may be absorbed more readily than large particles. Difference in particle size may account for why other researchers have estimated much longer biological half-times of months to years for exposures to presumably relatively insoluble nickel compounds of larger particle size (Torjussen and Andersen, 1979: Boysen *et al.*, 1984; Åkesson and Skerfving, 1985). The precise role that particle size or dose may play in the absorption and excretion of insoluble nickel compounds in humans is still uncertain (Sunderman *et al.*, 1986).

Reported urinary excretion half-times following oral exposures are similar to those reported for inhalation (Christensen and Lagesson, 1981; Sunderman *et al.*, 1989). Christensen and Lagesson (1981) reported that maximal excretion of nickel in urine occurred within the first 8 hours of ingesting soluble nickel compounds. The highest daily maximum renal excretion reported by the authors was 0.5 mg Ni/day.

Excretion *via* other routes is somewhat dependent on the form of the nickel compound absorbed and the route of exposure. Unabsorbed dietary nickel is lost in feces. Insoluble particles cleared from the lung *via* mucociliary action and deposited in the gastrointestinal tract are also excreted in the feces.

Sweat constitutes another elimination route of nickel from the body; nickel concentrations in sweat have been reported to be 10 to 20 times higher than concentrations in urine (Cohn and Emmett, 1978; Christensen *et al.*, 1979). Sunderman *et al.* (1986) state that profuse sweating may account for the elimination of a significant amount of nickel.

Bile has been shown to be an elimination route in laboratory animals, but its importance as an excretory route in humans is unknown.

Hair is also an excretory tissue of nickel. However, use of hair as an internal exposure index has not gained wide acceptance due to problems associated with external surface contamination and non-standardized cleaning methods (IPCS, 1991).

Nickel may also be excreted in human breast milk leading to dietary exposure of breast-fed infants. On a body weight basis, such exposures are

believed to be similar to average adult dietary nickel intake (Grandjean, 1984).

4.5 Factors Affecting Metabolism

Some disease states and physiological stresses have been shown to either increase or decrease endogenous nickel concentrations. As reviewed by Sunderman *et al.* (1986) and the U.S. Environmental Protection Agency (U.S. EPA, 1986), serum nickel concentrations have been found to be elevated in patients after myocardial infarction, severe myocardial ischemia, or acute stroke. Serum nickel concentrations are often decreased in patients with hepatic cirrhosis, possibly due to hypoalbuminemia (McNeely *et al.*, 1971). Physiological stresses such as acute burn injury have been shown to correspond with increased nickel serum levels in rats. Animal studies also indicate that nickel may be an endogenous vasoactive substance and that low concentrations (0.1 µM) of nickel chloride can induce coronary vasoconstriction in the perfused hearts of rats (Edoute *et al.*, 1992).

5. Toxicity Of Nickel Compounds

The major routes of nickel exposure that have toxicological relevance to the workplace are inhalation and dermal exposures. Oral exposures can also occur (*e.g.,* hand to mouth contact), but the institution of good industrial hygiene practices (*e.g.,* washing hands before eating) can greatly help to minimize such exposures. Therefore, this chapter mainly focuses on the target systems affected by the former routes (*i.e.,* the respiratory system and the skin). To the extent that other routes (such as oral exposures) may play a role in the overall toxicity of nickel and its compounds, these routes are also briefly mentioned. Focus is on the individual nickel species most relevant to the workplace, namely, metallic nickel and nickel alloys, oxidic, sulfidic and soluble nickel compounds, and nickel carbonyl.

5.1 Metallic Nickel

Occupational exposure to metallic nickel can occur through a variety of sources. Most notable of these sources are metallurgical operations, including stainless steel manufacturing, nickel alloy production, and related powder metallurgy operations. Other sources of potential occupational exposure to metallic nickel include nickel-cadmium battery manufacturing, chemical and catalyst production, plating, and miscellaneous applications such as coin production. In nearly all cases, metallic nickel exposures include concomitant exposures to other nickel compounds (most notably oxidic nickel, but other nickel compounds as well), and can be confounded with exposure to toxic non-nickel materials. Therefore, it is important to summarize those health effects which can most reasonably and reliably be considered relevant to metallic nickel in occupational settings, despite the fact that other nickel and non-nickel compounds may be present.

5.1.1 Inhalation Exposure: Metallic Nickel

With respect to inhalation, the only significant health effects seen in workers occupationally exposed to metallic nickel occur in the respiratory system. The two potential effects of greatest concern with respect to metallic nickel exposures are non-malignant respiratory effects (including asthma and fibrosis) and respiratory cancer. Factors that can influence these effects include: the presence of particles on the bronchio-alveolar surface of lung tissue, mechanisms of lung clearance (dependent on solubility), mechanisms of cellular uptake (dependent on particle size, particle surface area, and particle charge) and, the release of Ni (II) ion to the target tissue (of importance to both carcinogenicity and Type I immune reactions leading to asthma).

In the case of respiratory cancer, studies of past exposures and cancer mortality reveal that respiratory tumors have not been consistently associated with all chemical species of nickel. Metallic nickel is one of the species for which this is true. Indeed, epidemiological data generally indicate that metallic nickel is not carcinogenic to humans. Over 40,000 workers from various nickel-using industry sectors (nickel alloy manufacturing, stainless steel manufacturing, and the manufacturing of barrier material for use in uranium enrichment) have been examined for evidence of carcinogenic risk due to exposure to metallic nickel and, in some instances, accompanying oxidic nickel compounds and nickel alloys (Cox *et al.*,1981; Polednak, 1981; Enterline and Marsh, 1982; Cragle *et al.,* 1984; Arena *et al.,* 1998; Moulin *et al.,* 2000). No nickel-related excess respiratory cancer risks have been found in any of these workers.

5. Toxicity Of Nickel Compounds

Of particular importance are the studies of Cragle *et al.* (1984) and Arena *et al.* (1998). The former study of 813 barrier manufacturing workers is important because of what it reveals specifically about metallic nickel. There was no evidence of excess respiratory cancer risks in this group of workers exposed solely to metallic nickel. The latter study is important because of its size (>31,000 nickel alloy workers) and, hence, its power to detect increased respiratory cancer risks. Exposures in these workers were mainly to oxidic and metallic nickel. Only a very modest relative risk of lung cancer (RR, 1.13; 95% CI 1.05-1.21) was seen in these workers when compared to the overall U.S. population. Relative risk of lung cancer was even lower (RR, 1.02; 95% CI 0.96-1.10) in comparison to local populations, the risk being statistically insignificant. The lack of a significant excess risk of lung cancer relative to local populations, combined with a lack of an observed dose response with duration of employment regardless of the comparison population used, suggests that other non-occupational factors associated with geographic residence or cigarette smoking may explain the modest elevation of lung cancer risk observed in this cohort (Arena *et al.*, 1998).

While occupational exposures to metallic nickel in the nickel-using industry have historically been low (<0.5 mg Ni/m^3), certain subgroups of workers, such as those in powder metallurgy, have been exposed to higher concentrations of metallic nickel (around 1.5 mg Ni/m^3) (Arena *et al.*, 1998). Such subgroups, albeit small in size, have shown no nickel-related excess cancer risks.

In studies of nickel-producing workers (over 6,000 workers) where exposures to metallic nickel have, in certain instances, greatly exceeded those found in the nickel-using industry, evidence of a consistent association between metallic nickel and respiratory cancer is lacking. For one of these cohorts, the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990) did not find an association between excess mortality risk for respiratory cancers and metallic nickel workers, whereas another group of researchers (Easton *et al.,* 1992) found a significant association using a multivariate regression model. However, the Easton *et al.* (1992) model substantially overpredicted cancer risks in long-term workers (>10 years) who were employed between the years 1930-1939. This led the researchers to conclude that they may have "*overestimated the risks for metallic (and possibly soluble) nickel and underestimated those for sulfides and/or oxides*" (Easton *et al.,* 1992). A recent update of hydrometallurgical workers with relatively high metallic nickel exposures confirms the lack of excess respiratory cancer risk associated with exposures to elemental nickel during refining (Egedahl *et al.,* 2001).

Animal data on carcinogenicity are largely in agreement with the human data. Early studies on the inhalation of metallic nickel powder, although somewhat limited with respect to experimental design, are essentially negative for carcinogenicity (Hueper, 1958; Hueper and Payne, 1962). While intratracheal instillation of nickel powder has been shown to produce tumors in the lungs or mediastinum of animals (Pott *et al.*, 1987; Ivankovic *et al.*, 1988), the relevance of such studies in the etiology of lung cancer in humans is questionable. This is because normal defense systems and clearance mechanisms operative via inhalation are by-passed in intratracheal studies. Moreover, high mortality in one of the studies (Ivankovic *et al.*, 1988) suggests that toxicity could have confounded the carcinogenic finding in this study. Recently, Driscoll *et al.*

(2000) have cautioned that, in the case of intratracheal instillation studies, care must be taken to avoid doses that are excessive and may result in immediate toxic effects to the lung due to a large bolus delivery.

To address the lack of proper inhalation studies with nickel metal powders and regulatory requests from the European Union and Germany, an inhalation carcinogenicity study was initiated by the Nickel Producers Environmental Research Association in 2004. This study was preceded by a 13-week inhalation study (Kirkpatrick, 2004) and a 4-week toxicity study (Kirkpatrick, 2002). The toxicity data from the 13-week study with nickel metal powder were used to select the exposure range in the carcinogenicity study.

The results of the definitive animal carcinogenicity study with inhalable nickel metal powder (~1.6 µMMAD) by inhalation in male and female Wistar rats was conducted using a 2-year regimen of exposure at 0, 0.1, 0.4, and 1 mg/m^3. Toxicity and lethality required the termination of the 1 mg/m^3. Nevertheless, the 0.4 mg/m^3 group established the required Maximum Tolerated Dose (MTD) for inhalation of nickel metal powder and hence, was valid for the determination of carcinogenicity. This study did not show an association between nickel metal powder exposure and respiratory tumors.

These data, in concert with the most recent epidemiological findings and a separate negative oral carcinogenicity study of water soluble nickel salts, strongly indicates that nickel metal powder is not likely to be a human carcinogen by any relevant route of exposure.

With respect to non-malignant respiratory disease, various cases of asthma, fibrosis, and decrements in pulmonary function have been reported in workers with some metallic nickel exposures. In the case of asthma, exposure to fine dust containing nickel has only infrequently been reported in anecdotal publications as a possible cause of occupational asthma (Block and Yeung, 1982; Estlander *et al.*, 1993; Shirakawa *et al.*, 1990). Such dust exposures, however, have almost certainly included other confounding agents. Furthermore, no quantitative relationship has been readily established between the concentration of nickel cations in aqueous solution in bronchial challenge tests and equipotent metallic nickel in the occupational environment. In a U.S. study of welders (exposed to fumes containing some metallic nickel as well as complex spinels and other metals) at a nuclear facility in Oak Ridge, Tennessee, no increased mortality due to asthma was found among the workers studied (Polednak, 1981). Collectively, therefore, the overall data for metallic nickel being a respiratory sensitizer are not compelling, although a definitive study is lacking.

In addition to the very small number of anecdotal case-reports regarding asthma, a few other respiratory effects due to metallic nickel exposures have also been reported. Data relating to respiratory effects associated with short-term exposure to metallic nickel are very limited. One report of a fatality involved a man spraying nickel using a thermal arc process (Rendall *et al.*, 1994). This man was exposed to very fine particles or fumes, likely consisting of metallic nickel or oxidic nickel. He died 13 days after exposure, having developed pneumonia, with post mortem showing of shock lung. However, the relevance of this case to normal daily occupational exposures is questionable given the reported extremely high exposure (382 mg Ni/m^3) to relatively fine nickel particles.

5. Toxicity Of Nickel Compounds

A few recent studies have investigated the effects of nickel exposure on pulmonary function and fibrosis. With respect to pulmonary function, the most relevant study to metallic nickel was that of Kilburn et al. (1990) who examined cross-shift and chronic pulmonary effects in a group of stainless steel welders (with some metallic nickel exposure). No differences in pulmonary function were observed in test subjects versus controls during cross-shift or short-term exposures. Although some reduced vital capacities were observed in long-term workers, the authors noted little evidence of chronic effects on pulmonary function caused by nickel. Conversely, in recent studies of stainless steel and mild steel welders, short-term, cross-shift effects were noted in stainless steel workers (reduced FEV_1:FVC[2] ratio), but no long-term effects in lung function were noted in workers with up to 20 years of welding activity (Sobaszek et al., 1998; 2000). A generalized decrease in lung function, however, was seen in workers with the longest histories (over 25 years) of stainless steel welding. This was attributed to the high concentrations of mixed pollutants (*i.e.,* dust, metals, and gasses) to which these welders were exposed. A higher prevalence of bronchial irritative symptoms, such as cough, was also reported.

With respect to fibrosis, a recent study on nickel refinery workers in Norway has shown some evidence of an increased risk of X-ray abnormalities (ILO ≥1/0) (Berge and Skyberg, 2001). Associations of radiologically-defined fibrosis with soluble and sulfidic nickel (but, also, possibly metallic nickel) were observed. However, it was noted that the associations were based on a small number of cases that were relatively mild in nature. Undetected confounders may have been present. Without further study of other nickel workers, the role of metallic nickel to induce pulmonary fibrosis remains unclear.

Animal studies on the non-carcinogenic respiratory effects of metallic nickel are few. The early studies by Heuper and Payne (1962) suggest that inflammatory changes in the lung can be observed in rats and hamsters administered nickel powder via inhalation. However, lack of details within the studies preclude drawing any conclusions with respect to the significance of the findings. More recent studies on the effects of ultrafine metallic nickel powder (mean diameter of 20 nm) administered intratracheally or via short-term inhalation in rats showed significant inflammation, cytotoxicity, and/or increased epithelial permeability of lung tissue (Zhang *et al.*, 1998; Serita *et al.*, 1999). While ultrafine metallic nickel powders are not widely produced or used at this time, their high level of surface energy, high magnetism, and low melting point are likely to make ultrafine metallic nickel powders desirable for future use in magnetic tape, conduction paste, chemical catalysts, electronic applications, and sintering promoters (Kyono *et al.*, 1992). Hence, the results of the above studies bear further watching. It should be noted that occupational exposures to metallic nickel are usually to larger size particles ("inhalable" size aerosol fraction, ≤100 µm particle diameter). In certain specific operations involving the manufacturing and packaging of finely divided elemental nickel powders ("respirable" size particles, ≤10 µm particle diameter) or ultrafine powders (<1 µm particle diameter) exposures to finer particles may occur. In these operations, special precautions to reduce inhalation exposure to fine and ultrafine metallic nickel powders should be taken.

Collectively, the above findings present a mixed picture with respect to the potential risk of non-malignant respiratory disease from metallic nick-

[2] *Forced Expiratory Volume (FEV_1) is the amount of air that you can forcibly blow out in one second, measured in litres. Forced vital capacity (FVC) is the amount of air that can be maximally forced out of the lungs after a maximal inspiration. The FEV to FVC ratio reflects the severity of pulmonary impairment in obstruction (healthy adults should be between 75-89%).*

el exposures. There is an extensive body of literature demonstrating that past exposures to metallic nickel have not resulted in excess mortality from such diseases (Cox *et al.*, 1981; Polednak, 1981; Enterline and Marsh, 1982; Cragle *et al.,* 1984; Egedhal *et al.*, 1993; 2001; Arena *et al.,* 1998; Moulin *et al.,* 2000). However, additional studies on such effects, particularly with respect to ultrafine nickel powders, would be useful.

5.1.2 Dermal Exposure: Metallic Nickel

Dermal exposure to metallic nickel is possible wherever nickel powders are handled, such as powder metallurgy, and in the production of nickel-containing batteries, chemicals, and catalysts. Occasional contact with massive forms of metallic nickel could occur during nickel plating (anodes) and coin manufacturing (nickel alloys).

Skin sensitization to nickel metal can occur wherever there is sufficient leaching of nickel ions from articles containing nickel onto exposed skin (Hemingway and Molokhita, 1987; Emmet *et al.*, 1988). However, cutaneous allergy (allergic contact dermatitis) to nickel occurs mainly as the result of non-occupational exposures. Indeed, in recent years, the evidence for occupationally-induced dermal nickel allergy is sparse (Mathur, 1984; Schubert *et al.*, 1987; Fischer, 1989).

Sensitization and subsequent allergic reactions to nickel require direct and prolonged contact with nickel-containing solutions or nickel-releasing items that are non-resistant to sweat corrosion (see further discussion under Sections 5.2 and 5.4). The nickel ion must be released from a nickel-containing article in intimate contact with skin to elicit a response. Evidence suggests that humid environments are more likely to favor the release of the nickel ion from metallic nickel and nickel alloys, whereas dry, clean operations with moderate or even intense contact to nickel objects will seldom, alone, provoke dermatitis (Fischer, 1989). In some occupations for which nickel dermatitis has been reported in higher proportion than the general populace (*e.g.,* cleaning, hairdressing and hospital wet work), the wet work is, in and of itself, irritating and decreases the barrier function of the skin. Often it is the combination of irritant dermatitis and compromised skin barrier that produces the allergic reaction (Fischer, 1989). The role of nickel in the manifestation of irritant dermatitis in metal manufacturing, cement and construction industries, and coin handling has been debated. It has been suggested by some researchers that nickel probably does not elicit dermatitis in workers from such industries unless the worker is already strongly allergic to nickel (Fischer, 1989). There are some reports that oral ingestion of high nickel levels (above 12 µg/kg/day) can trigger a dermatitis response in susceptible nickel-sensitized individuals (see section 5.3.3).

5.2 Nickel Alloys

Often there is a misconception that exposure to nickel-containing alloys is synonymous with exposure to metallic nickel. This is not true. Each type of nickel-containing alloy is a unique substance with its own special physico-chemical and biological properties that differ from those of its individual metal constituents. The potential toxicity of a nickel alloy (including carcinogenic effects) must, therefore, be evaluated separately from the potential toxicity of nickel metal itself and other nickel-containing alloys. While there are hundreds of different nickel-contain-

ing alloys in different product categories, the major product categories are stainless steel (containing Fe, Cr and up to 34% Ni) and high nickel content alloys. Occupational exposures to these and other forms of nickel alloys (*e.g.,* superalloys, cast-irons) can occur wherever alloys are produced (metallurgical operations) or in the processing of alloys (such as welding, grinding, cutting, polishing, and forming). As in the case of metallic nickel, occupational exposures to nickel-containing alloys will mainly be via the skin or through inhalation. However, in the case of certain nickel alloys that are used in prosthetic devices, localized exposures can occur. Because such exposures are not of specific concern to occupational settings, they are not discussed in this Guide. However, a comprehensive review of information pertaining to prosthetic devises can be found in McGregor *et al.* (2000).

5.2.1 Inhalation Exposure: Nickel Alloys

There are no studies of nickel workers exposed solely to nickel alloys in the absence of metallic or oxidic nickel. Clearly, however, workers in alloy and stainless steel manufacturing and processing will likely have some low level exposure to nickel alloys. In general, most studies on stainless steel and nickel alloy workers have shown no significant occupationally-related excess risks of respiratory cancer (Cox *et al.*, 1981; Polednak, 1981; Cornell, 1984; Svensson *et al.*, 1989; Moulin *et al.,* 1993, 2000; Hansen *et al.*, 1996; Jakobsson *et al.,* 1997; Arena *et al.,* 1998). There have been some exceptions, however, in certain groups of stainless steel welders (Gerin *et al.*, 1984; Kjuus *et al.*, 1986) where excess lung tumors were detected. Further analyses of these and other stainless steel workers as part of a large international study on welders (>11,000 workers) failed to show any association between increased lung cancer mortality and cumulative exposure to nickel (Siminato *et al.*, 1991). A later analysis of this same cohort (Gerin *et al.,* 1993) showed no trend for lung cancer risk for three levels of nickel exposure. Likewise, no nickel-related tumors were observed in a group of German arc welders exposed to fumes containing chromium and nickel (Becker, 1999). As noted above and in the discussion on metallic nickel, some of these studies involved thousands of workers (Arena *et al.,* 1998; Siminato *et al.*, 1991). Hence, these studies suggest an absence of nickel-related excess cancer risks in workers exposed to nickel-containing alloys.

Limited data are available to evaluate respiratory carcinogenicity of nickel alloys in animals. One intratracheal instillation study looked at two types of stainless steel grinding dust. An austenitic stainless steel (6.8% nickel) and a chromium ferritic steel (0.5% nickel) were negative in hamsters after repeated instillations (Muhle *et al.,* 1992). In another study, grinding dust from an austenitic stainless steel (26.8% nickel) instilled in hamsters was also negative (Ivankovic *et al.,* 1988). In this same study, an alloy containing 66.5% nickel, 12.8% chromium, and 6.5% iron showed some evidence of carcinogenic potential at the higher doses tested. A significant shortening in survival time in one of the high dose groups compared to untreated controls, however, raises the question of toxicity and its possible confounding effect on tumor formation. As noted in the discussion of metallic nickel, intratracheal instillation studies must be carefully interpreted in light of their artificial delivery of unusually large and poten-

tially toxic doses of chemical agents to the lung (Driscoll *et al.*, 2000).

In total, there is little evidence to suggest that nickel alloys act as respiratory carcinogens. For many alloys, this may be due to their corrosion resistance which results in reduced release of metal ions to target tissues.

With respect to non-carcinogenic respiratory effects, no animal data are available for determining such effects, and the human studies that have looked at such endpoints have generally shown no increased mortality due to non-malignant respiratory disease (Polednak, 1981; Cox *et al.*, 1981; Simonato *et al.*, 1991; Moulin *et al.,* 1993, 2000; Arena *et al.,* 1998).

5.2.2 Dermal Exposure: Nickel Alloys

Because alloys are specifically formulated to meet the need for manufactured products that are durable and corrosion resistant, an important property of all alloys and metals is that they are insoluble in aqueous solutions. They can, however, react (corrode) in the presence of other media, such as air or biological fluids, to form new metal-containing species that may or may not be water soluble. The extent to which alloys react is governed by their corrosion resistance in a particular medium and this resistance is dependent on the nature of the metals, the proportion of the metals present in the alloy, and the process by which the alloy was made.

Of particular importance to dermal exposures are the potential of individual alloys to corrode in sweat. As noted under the discussion of metallic nickel, sensitization and subsequent allergic reactions to nickel require direct and prolonged contact with nickel-containing solutions or materials that are non-resistant to sweat corrosion. It is the release of the nickel (II) ion, not the nickel content of an alloy, that will determine whether a response is elicited. Occupational dermal exposures to nickel alloys are possible wherever nickel alloy powders are handled, such as in powder metallurgy or catalyst production. While exposures to massive forms of nickel alloys are also possible in occupational settings, these exposures do not tend to be prolonged, and, hence, are not of greatest concern with respect to contact dermatitis. Dermal contact with nickel-copper alloys in coinage production can also occur. The potential for nickel alloys to elicit an allergic reaction in occupational settings, therefore, will depend on both the sweat resistant properties of the alloy and the amount of time that a worker is in direct and prolonged contact with an alloy.

The European Union has adopted a Directive (94/27/EC) that is designed to protect most consumers against the development of nickel dermal sensitization through direct and prolonged contact with nickel-containing articles (EC, 1999). With the exception of ear-piercing materials, which are limited to <0.05% nickel content, other nickel-containing articles are regulated based upon the amount of nickel released into "artificial sweat." Only metals and alloys that release less than 0.5 microgram of nickel per square centimeter per week are allowed to be used in such articles. While determination of individual nickel alloys to meet this standard requires testing on a case-by-case basis, it is worth noting that recent studies of nickel release from stainless steels (AISI 303, 304, 304L, 316, 316L, 310S, 430) in artificial sweat medium have shown that the only grade of stainless steel for which the nickel release rates were close to or exceeded the 0.5 $\mu g/cm^2$/

week limit is type 303 (a special stainless steel type with elevated sulfur content to aid machinability). All other grades of stainless steel demonstrated negligible nickel release, in all cases less than 0.3 µg Ni/cm^2/week (Haudrechy *et al.,* 1994). Although the EU Nickel Directive aims at preventing dermatitis in most nickel sensitized patients, there are some extremely sensitive subjects that have shown positive patch test results with nickel alloys (non-stainless steels) that release 0.5 µg Ni/cm^2/week or less (Gawkrodger, 1996). With these few exceptions, the use of 0.5 µg Ni/cm^2/week seems to be protective for the majority of nickel-allergic patients.

While the EU Nickel Directive is geared toward protecting the public from exposures to nickel contained in consumer items, it may also provide some guidance in occupational settings where exposures to nickel alloys are direct and prolonged. It should be noted, however, that alloys that release greater than 0.5 ug/cm^2/week of nickel may not be harmful in an occupational or commercial setting. They may be used safely when not in direct and prolonged contact with the skin or where ample protective clothing is provided. A recent comprehensive review of the health effects associated with the manufacture, processing, and use of stainless steel can be found in Cross *et al.* (1999).

5.3 Soluble Nickel

Exposure to readily water soluble nickel salts occurs mainly during the electrolytic refining of nickel (producing industries) and in electroplating (using industries). Depending upon the processes used, exposures are usually to hydrated nickel (II) sulfate or nickel chloride in solution. As with the previously mentioned nickel species, the routes of exposure of toxicological relevance to the workplace are inhalation and dermal exposures. However, unlike other nickel species, soluble nickel occurs in food and water; thus, oral exposures are briefly mentioned below.

5.3.1 Inhalation Exposure: Soluble Nickel

As in the case of metallic nickel, the two effects of greatest concern for the inhalation of soluble nickel compounds are non-malignant respiratory effects (*e.g.*, fibrosis, asthma) and respiratory cancer. Unlike metallic nickel, however, which has shown little evidence of carcinogenicity, the carcinogenic assessment of soluble nickel compounds has been somewhat controversial, with no consensus in the scientific community regarding the appropriate classification of soluble nickel as a carcinogen (ICNCM, 1990; IARC, 1990; ACGIH, 1998; BK-Tox, 1999; Haber, 2000a and b). As a result, some groups view soluble nickel as a "known" carcinogen; others view the evidence for carcinogenicity data as "not classifiable" or "indeterminable." It should be noted that under the Existing Substances regulations in Europe water-soluble nickel compounds have been classified as "known human carcinogens" but only by the inhalation route of exposure. The problem lies both in reconciling what appears to be inconsistent human data and in interpreting the human and animal data in an integrated manner that provides a cohesive picture of the carcinogenicity of soluble nickel compounds (Oller, 2002).

Human evidence for the carcinogenicity of soluble nickel compounds comes mainly from studies of nickel refinery workers in Wales, Norway, and Finland (Peto *et al.,* 1984; ICNCM, 1990;

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Easton *et al.*, 1992; Andersen *et al.*, 1996; Anttila *et al.*, 1998). In these studies, workers involved in electrolyses, electrowinning, and hydrometallurgy have shown excess risks of lung and/or nasal cancer. Exposures to soluble nickel have generally been believed to be high in most of these workers (in excess of 1 mg Ni/m^3), although some studies have suggested that exposures slightly lower than 1 mg Ni/m^3 may have contributed to some of the cancers observed (Anttila *et al.*, 1998; Grimsrud, 2003). In all instances, soluble nickel exposures in these workers have been confounded by concomitant exposures to other nickel compounds (notably, oxidic and sulfidic nickel compounds), other chemical agents (*e.g.*, soluble cobalt compounds, arsenic, acid mists) or cigarette smoking-all known or believed to be potential carcinogens in and of themselves (see Sections 5.4 and 5.5). Therefore, it is unclear whether soluble nickel, alone, caused the excess cancer risks seen in these workers.

In contrast to these workers, electrolysis workers in Canada and plating workers in the U.K. have shown no increased risks of lung cancer (Roberts *et al.*, 1989; ICNCM, 1990; Pang, *et al.*, 1996). In the case of the Canadian electrolyses workers, their soluble nickel exposures were similar to those of the electrolysis workers in Norway. Soluble nickel exposures in the plating workers, although unknown, are presumed to have been lower. On the whole, these workers were believed to lack, or have lower exposures to, some of the confounding agents present in the work environments of the workers mentioned above. While nasal cancers were seen in a few of the Canadian electrolysis workers, these particular workers had also worked in sintering departments where exposures to sulfidic and oxidic nickel were very high (>10 mg Ni/m^3). It is likely that exposures to the latter forms of nickel (albeit some of them short) may have contributed to the nasal cancers observed (see Sections 5.4 and 5.5).

Besides the epidemiological studies, the animal data also needs to be considered. The most important inhalation animal studies conducted to date are those of the U.S. National Toxicology Program. In these studies, nickel subsulfide, nickel sulfate hexahydrate, and a high-temperature nickel oxide were administered to rats and mice in two-year carcinogenicity bioassays (NTP, 1996a, 1996b, 1996c). Results from the nickel sulfate hexahydrate study (1996b) are particularly pertinent to the assessment of the carcinogenicity of soluble nickel compounds. This 2-year chronic inhalation study failed to produce any carcinogenic effects in either rats or mice at exposures to nickel sulfate hexahydrate up to 0.11 mg Ni/m^3 or 0.22 mg Ni/m^3, respectively (NTP, 1996b). These concentrations correspond to approximately 2 or 6 mg Ni/m^3 workplace aerosols after adjusting for particle size and animal to human extrapolation (Hsieh *et al.,* 1999; Yu *et al.,* 2001). It is also worth noting that soluble nickel compounds administered via other relevant routes of exposure (oral) have also failed to produce tumors (Schroeder *et al.*, 1964, 1974; Schroeder and Mitchener, 1975; Ambrose *et al.*, 1976).

In sum, the negative animal data combined with the conflicting human data make for an uncertain picture regarding the carcinogenicity of soluble nickel alone.

As recently noted by Oller (2002), without a unifying mechanism that can both account for the discrepancies seen in the human data and integrate the results from human and animal data into a single model for nickel respiratory carcinogenesis, assessments of soluble nickel will continue to vary widely. Such a mechanism has been

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proposed in models for nickel-mediated induction of respiratory tumors. These models suggest that the main determinant of the respiratory carcinogenicity of a nickel species is likely to be the bioavailability of the nickel (II) ion at nuclear sites of target epithelial cells (Costa, 1991; Oller *et al.*, 1997; Haber *et al.,* 2000a). Only those nickel compounds that result in sufficient amounts of bioavailable nickel (II) ions at such sites (after inhalation) will be respiratory carcinogens. Because soluble nickel compounds are not phagocytized and are rapidly cleared, substantial amounts of nickel (II) ions that would cause tumor induction simply are not present.

However, at workplace-equivalent levels above 0.1 mg Ni/m^3, chronic respiratory toxicity was observed in animal studies. Respiratory toxicity due to soluble nickel exposures may have enhanced the induction of tumors by less soluble nickel compounds or other inhalation carcinogens seen in refinery workers. This may account for the observed respiratory cancers seen in the Norwegian, Finnish, and Welsh refinery workers who had concomitant exposures to smoking and other inhalation carcinogens. Indeed, in its multi-analysis of many of the nickel cohorts discussed above, the International Committee on Nickel Carcinogenesis in Man (ICNCM) postulated that the effects of soluble nickel may be to enhance the carcinogenic process, as opposed to inducing it (ICNCM, 1990). Alternatively, it should be considered that none of the workers in the sulfidic ores refinery studies had pure exposures to soluble nickel compounds that did not include sulfidic or complex nickel oxides, and most of them had exposures which were confounded by smoking, exposure to arsenic, or both.

Animal inhalation studies have shown various non-malignant respiratory effects on the lung following relatively short periods of exposure to relatively high levels of soluble nickel compounds (Bingham *et al.*, 1972; Murthy *et al.*, 1983; Berghem *et al.*, 1987; Benson *et al.*, 1988; Dunnick *et al.*, 1988,1989). Effects have included marked hyperplasia, inflammation and degeneration of bronchial epithelium, increased mucus secretion, and other indicators of toxic damage to lung tissue. In a recent study where nickel sulfate was administered via a single intratracheal instillation in rats, the nickel sulfate was shown to affect pulmonary antitumoral immune defenses transiently (Goutet *et al.*, 2000). Chronic exposures to nickel sulfate hexahydrate result in cell toxicity and inflammation (NTP, 1996b). Moreover, a recent subchronic study demonstrated that nickel sulfate hexahydrate has a steep dose-response for toxicity and mortality (Benson *et al.*, 2001). Hence, although exposure to soluble nickel compounds, alone, may not provide the conditions necessary to cause cancer (*i.e.,* the nickel (II) ion is not delivered to the target tissue in sufficient quantities *in vivo*), due to their toxicity, soluble nickel compounds may enhance the carcinogenic effect of certain other nickel compounds or cancer causing agents by increasing cell proliferation. Cell proliferation, in turn, is required to convert DNA lesions into mutations and expand the mutated cell population, resulting in carcinogenesis.

With respect to non-malignant respiratory effects in humans, the evidence for soluble nickel salts being a causative factor for occupational asthma, while not overwhelming, is more suggestive than it is for other nickel species. Such evidence arises mainly from a small number of case reports in the electroplating industry and nickel catalyst manufacturing (McConnell *et al.*, 1973; Malo *et al.*, 1982, 1985; Novey *et al.*, 1983; Davies, 1986; Bright *et al.*, 1997).

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Exposure to nickel sulfate can only be inferred in some of the cases where exposures have not been explicitly stated. Many of the plating solutions and, hence, aerosols to which some of the workers were exposed may have had a low pH. This latter factor may contribute to irritant effects which are not necessarily specific to nickel. In addition, potential for exposure to other sensitizing metals, notably chromium and cobalt, may have occurred. On the basis of the studies reported, the frequency of occupational asthma cannot be assessed, l*et al*one the dose response determined. Despite these shortcomings, however, the role of soluble nickel as a possible cause of asthma should be considered.

Aside from asthma, the only other non-carcinogenic respiratory effect reported in nickel workers is that of fibrosis. Evidence that soluble nickel may act to induce pulmonary fibrosis comes from a recent study of nickel refinery workers that showed modest abnormalities in the chest X-rays of workers (Berge and Skyberg, 2001). An association between the presence of irregular opacities (ILO ≥1/0) in chest X-rays and cumulative exposures to soluble nickel, sulfidic nickel, and possibly metallic nickel, was reported. The significance of these results for the clinical diagnosis of fibrosis remains to be determined.

5.3.2 Dermal Exposure: Soluble Nickel

Historically, risks for allergic contact nickel dermatitis have been elevated in workplaces where exposures to soluble nickel have been high. For example, nickel dermatitis was common in the past among nickel platers. However, due to improved industrial and personal hygiene practices, more recent reports of nickel sensitivity in workplaces such as the electroplating industry have been sparse (Mathur, 1984; Fischer, 1989). Schubert *et al.*, (1987) found only two nickel sensitive platers among 176 nickel sensitive individuals studied. A number of studies have shown nickel sulfate to be a skin sensitizer in animals, particularly in guinea pigs (Lammintausta *et al.*, 1985; Zissu *et al.*, 1987; Rohold *et al.*, 1991; Nielsen *et al.*, 1992). Dermal studies in animals suggest that sensitization to soluble nickel (nickel sulfate) may result in cross sensitization to cobalt (Cavelier *et al.*, 1989) and that oral supplementation with zinc may lessen the sensitivity reaction of $NiSO_4$-induced allergic dermatitis (Warner *et al.*, 1988). Five percent nickel sulfate in petrolatum is typically used in patch tests as the threshold for elicitation of a positive skin reaction, although individual thresholds may vary (Uter *et al.*, 1995). Soluble nickel compounds should be considered skin sensitizers in humans and care should be taken to avoid prolonged contact with nickel solutions in the workplace.

5.3.3 Other Exposures: Soluble Nickel

Existing data on the oral carcinogenicity of nickel substances have been historically inconclusive, yet, the assessment of the oral carcinogenicity potential of nickel has serious scientific and regulatory implications. In a study by Heim *et al.* (2007), nickel sulfate hexahydrate was administered daily to rats by oral gavage for two years (104 weeks) at exposure levels of 10, 30 and 50 mg $NiSO_4 \cdot 6H_2O$/kg. This treatment produced a statistically significant reduction in body weight of male and female rats, compared to controls, in an exposure-related fashion at 30 and 50 mg/kg/day. An exposure-dependent increase in mortality was observed in female rats. However, daily oral

administration of nickel sulfate hexahydrate did not produce an exposure-related increase in any common tumor type or an increase in any rare tumors. This study achieved sufficient toxicity to reach the Maximum Tolerated Dose (MTD) while maintaining a sufficiently high survival rate to allow evaluation for carcinogenicity. The study by Heim *et al.* (2007) demonstrates that nickel sulfate hexahydrate does not have the potential to cause carcinogenicity by the oral route of exposure. *Data from this and other studies demonstrate that inhalation is the only route of exposure that might cause concern for cancer in association with nickel compound exposures.*

Unlike other species of nickel, oral exposure to soluble nickel occurs from drinking water and food. Data from both human and animal studies show that absorption of nickel from food and water is generally low (1-30%), depending on the fasting state of the subject, with most of the nickel excreted in feces (Diamond *et al.*, 1998). In humans, effects of greatest concern for ingested nickel are those produced in the kidney, possible reproductive effects, and the potential for soluble nickel to exacerbate nickel dermatitis following oral provocation.

Several researchers have examined the evidence of nephrotoxicity related to long-term exposures of soluble nickel in electroplating, electrorefining and chemical workers (Wall and Calnan, 1980; Sunderman and Horak, 1981; Sanford and Nieboer, 1992; Vyskoďl et al., 1994). These workers not only would have been exposed to soluble nickel in their food and water, but also in the workplace air which they breathed. Wall and Calnan (1980) found no evidence of renal dysfunction among 17 workers in an electroplating plant. Likewise, Sanford and Nieboer (1992), in a study of 26 workers in electrolytic refining plants, concluded that nickel, at best, might be classified as a mild nephrotoxin. In the Sunderman and Horak study (1981) and the Vyskočil et al., study (1994), elevated markers of renal toxicity (e.g., β2 microglobulin) were observed, but only spot urinary nickel samples were taken. The chronic significance of these effects is uncertain. In addition, nickel exposures were quite high in these workers (up to 13 mg Ni/m3 in one instance), and certainly not typical of most current occupational exposures to soluble nickel. Severe proteinuria and other markers of significant renal disease that have been associated with other nephrotoxicants (e.g., cadmium) have not been reported in nickel workers, despite years of biological monitoring and observation (Nieboer et al., 1984).

In regard to reproductive effects, there is some evidence in humans to indicate that absorbed nickel may be able to move across the placenta into fetal tissue (Creason *et al.*, 1976; Casey and Robinson, 1978; Chen and Lin, 1998; Haber *et al.*, 2000b). Because of this, the preliminary results from a study of Russian nickel refinery workers that purported to show evidence of spontaneous abortions, stillbirths, and structural malformations in babies born to female workers at that refinery deserved careful attention (Chashschin *et al.*, 1994). Concerns about the reliability of the Chashschin *et al.* (994) study prompted a more thorough and well-conducted epidemiology study to determine whether the effects observed in the Russian cohort were really due to their workplace nickel exposures or to other confounders in the workplace and/or ambient environment. The investigation of the reproductive health of the Russian cohort was important for another reason. Specifically, the nickel refineries in this region are the only places worldwide where enough female nickel refinery

workers exist to perform an epidemiological survey of reproductive performance compared to nickel exposure. In order to accomplish this task the researchers constructed a birth registry for all births occurring in the region during the period of the study. They also reconstructed an exposure matrix for the workers at the refineries so as to be able to link specific pregnancy outcomes with occupational exposures. The study culminated in a series of manuscripts by A. Vaktskjold *et al.* describing the results of the investigation. The study demonstrated nickel exposure was not correlated with adverse pregnancy outcome for 1) male newborns with genital malformations, 2) spontaneous abortions, 3) small-for-gestational-age newborns, or 4) musculosketal effects in newborns of female refinery workers exposed to nickel. These manuscripts showed no correlation between nickel exposure and observed reproductive impairment.

These are important results as spontaneous abortion in humans would most closely approximate the observation of perinatal lethality associated with nickel exposure in rodents. Further evidence that nickel exposure is not adversely affecting the reproduction of these women is provided by the lack of a "small-for-gestational-age" finding and also the lack of an association of male genital malformations with nickel exposure. Both of these findings are considered "sentinel" effects (*i.e.,* sensitive endpoints) for reproductive toxicity in humans.

The work by Vaktskjold *et al.* (2006, 2007, 2008a, 2008b) is important in demonstrating that any risk of reproductive impairment from nickel exposure is exceedingly small. However, it should be noted that it is not possible to find women whose occupational nickel exposure persisted throughout their pregnancies until birth. Generally, fetal protection policies require removal of pregnant women from jobs with exposures to possible reproductive toxicants. Therefore, it cannot be concluded that occupational exposure to nickel compounds during pregnancy presents no risk, only a risk that is exceedingly small.

With respect to animal studies, a variety of developmental, reproductive, and teratogenic effects have been reported in animals exposed mainly to soluble nickel via oral and parenteral administration (Haber *et al.*, 2000b). However, factors such as high doses, relevance of routes of exposure, avoidance of food and water, lack of statistical significance, and parental mortality have confounded the interpretation of many of the results (Nieboer, 1997; Haber *et al.*, 2000b). In the most recent and reliable reproductive study conducted to date, rats were exposed to various concentrations of nickel sulfate hexahydrate by gavage. In the 1-generation range finding study, evaluation of post-implantation/perinatal lethality among the offspring of the treated parental rats (*i.e.,* number of pups conceived minus the number of live pups at birth) showed statistically significant increases at the 6.6 mg Ni/kg/day exposure level and questionable increases at the 2.2 and 4.4 mg Ni/kg/day levels. The definitive 2-generation study demonstrated that these effects were not evident at concentrations up to 1.1 mg Ni/kg/day soluble nickel and were equivocally increased at 2.2 mg Ni/kg/day soluble nickel. No nickel effects on fertility, sperm quality, estrous cycle and sexual maturation were found in these studies (NiPERA, 2000).

Allergic contact dermatitis is the most prevalent effect of nickel in the general population. Epidemiological investigation showed that 20% of young (15-34 years) Danish women and 10% of older (35-69 years) women were nickel-sensi-

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tized, compared with only 2-4% of Danish men (15-69 years) (Nielsen and Menné, 1992). The prevalence of nickel allergy was found o be 7-10% in previously published reports (Menné *et al.*, 1989). EDTA reduced the number and severity of patch test reactions to nickel sulfate in nickel-sensitive subjects (Allenby and Goodwin, 1983).

Systemically induced flares of dermatitis have been reported after oral challenge of nickel-sensitive women with 0.5-5.6 mg of nickel as nickel sulfate administered in a lactose capsule (Veien, 1987). At the highest nickel dose (5.6 mg), there was a positive reaction in a majority of the subjects; at 0.5 mg, only a few persons responded with flares. Responses to oral doses of 0.4 or 2.5 mg of nickel did not exceed responses in subjects given placebos in double-blind studies (Jordan and King, 1979; Gawkrodger *et al.*, 1986).

There are several reports on the effects of diets low or high in nickel, but it is still a matter of discussion whether naturally occurring nickel in food may worsen or maintain the hand eczema of nickel-sensitive patients, mainly because results from dietary depletion studies have been inconclusive (Veien and Menné, 1990). In a single-blind study, 12 nickel-sensitive women 74ere challenged with a supplementary high-nickel diet (Nielsen *et al.*, 1990). The authors concluded that hand eczema was aggravated during the period (*i.e.,* days 0-11) and that the symptoms thus were nickel-induced. However, it should be noted that in some subjects the severity of the eczema (*i.e.,* the number of vesicles in the palm of the hand) varied markedly between day 14 or 21 before the challenge period and the start of the challenge period.

Oral hyposensitization to nickel was reported after six weekly doses of 5 mg of nickel in a capsule (Sjövall *et al.*, 1987) and 0.1 ng of nickel sulfate daily for 3 years (Panzani *et al.*, 1995). Cutaneous lesions were improved in eight patients with contact allergy to nickel after oral exposure to 5 mg of nickel weekly for 8 weeks (Bagot *et al.*, 1995). Nickel in water (as nickel sulfate) was given to 25 nickel-sensitive women in daily doses of 0.01-0.04 mg/kg of body weight per day for 3 months after they had been challenged once with 2.24 mg of nickel (Santucci *et al.*, 1988). In 18 women, flares occurred after the challenge dose, whereas only 3 out of 17 subjects had symptoms during the prolonged exposure period. Later, Santucci and coworkers (1994) gave increasing oral doses of nickel in water (0.01-0.03 mg of nickel per kg of body weight per day) to eight nickel-sensitive women for up to 178 days. A significant improvement in hand eczema was observed in all subjects after 1 month.

The Lowest Observed Adverse Effects Level (LOAEL) established after oral provocation of patients with empty stomachs was reported as 12 µg/kg of body weight (Nielsen *et al.*, 1999). However, this study sought to evaluate exacerbation of hand eczema which positions these results as occurring in probably the most sensitive human population possible. This figure was similar to the dose found in a study by Hindsén *et al.* (2001), where a total dose of 1 mg (17 µg/kg of body weight) was reported to result in a flare-up of dermatitis in an earlier patch test site in two of ten nickel-sensitive patients. The dose of 12 µg/kg of body weight was considered to be the acute LOAEL in fasting patients on a 48-hour diet with reduced nickel content. A cumulative LOAEL could be lower, but a LOAEL in non-fasting patients is probably higher because of reduced absorption of nickel ions when mixed in food.

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With respect to oral provocations of nickel dermatitis, it should be noted that nickel dermatitis via oral exposures only occurs in individuals already sensitized to nickel via dermal contact. The literature is not definitive with respect to the nickel concentration required to elicit a dermatitic response. However, collectively, studies suggest that only a minor number of nickel sensitive patients react to oral doses below 1.25 mg of nickel (~20 µg Ni/kg) (Menné and Maibach, 1987; Haber *et al.*, 2000b). These doses are in addition to the normal dietary nickel intake (~160 µg Ni/day).

Conversely, oral exposure to nickel in non-nickel-sensitized individuals has been shown to provide tolerance to future dermal nickel sensitization. Observations first made in animal experiments (Vreeburg *et al.,* 1984) and correlations obtained from studies of human cohorts (van der Burg *et al.,* 1986) led to the hypothesis that nickel hypersensitivity reactions may be prevented by prior oral exposure to nickel if long-term, low-level antigenic contact occurs in the non-sensitized organism. Studies that followed van der Burg's initial observation of induced nickel tolerance in humans have repeatedly confirmed the occurrence of this phenomenon both in humans (Kerosuo *et al.,* 1996; Todd and Burrows, 1989; van Hoogstraten *et al.,* 1991a; van Hoogstraten *et al.,* 1989; van Hoogstraten *et al.,* 1991b) and animals (van Hoogstraten *et al.,* 1992; van Hoogstraten *et al.,* 1993). Suppression of dermal nickel allergic reactions can also be achieved in sensitized individuals (Sjövall *et al.,* 1987).

5.4 Oxidic Nickel

The term "oxidic nickel" includes nickel (II) oxides, nickel (III) oxides, possibly nickel (IV) oxides and other non-stochiometric entities, complex nickel oxides (including spinels in which other metals such as copper, chromium, or iron are present), silicate oxides (garnierite), hydrated oxides, hydroxides, and, possibly, carbonates or basic carbonates which are subject to various degrees of hydration. Therefore, for the purposes of this document they will be considered together.

Oxidic nickel is used in many industrial applications and will be present in virtually every major nickel industry sector (NiPERA, 1996). Nickel oxide sinter is often the end product in the roasting of nickel sulfide concentrates. It is used as charge to produce wrought stainless steel and other alloy materials. It is also used in cast stainless steel and nickel-based alloys. Commercially available nickel oxide powders are used in the electroplating industry, for catalysis preparation, and for other chemical applications. Black nickel oxide and hydroxide are used in the production of electrodes for nickel-cadmium batteries utilized in domestic markets and also in large power units. Complex nickel oxides are used in oil refining and ceramic magnets (Thornhill, 2000; Van Vlack, 1980).

As in the case of the previously discussed nickel species, inhalation of oxidic nickel compounds is the route of exposure of greatest concern in occupational settings. Unlike the former species of nickel, however, dermal exposures to oxidic nickel are believed to be of little consequence to nickel workers. While no data are directly available on the effects of oxidic nickel compounds on skin, due to their low water solubility, very low absorption of nickel through the skin is expected.

5.4.1 Inhalation Exposure: Oxidic Nickel

The critical health effect of interest in relation to occupational exposure to oxidic nickel is, again, respiratory cancer. Unlike metallic nickel, which does not appear to be carcinogenic, and soluble nickel, whose carcinogenic potential is still open for debate, the evidence for the carcinogenicity of certain oxidic nickel compounds is more compelling. That said, there is still some uncertainty regarding the forms of oxidic nickel that induce tumorigenic effects. Although oxidic nickel is present in most major industry sectors, it is of interest to note that epidemiological studies have not consistently implicated all sectors as being associated with respiratory cancer. Indeed, excess respiratory cancers have been observed only in refining operations in which nickel oxides were produced during the refining of sulfidic ores and where exposures to oxidic nickel were relatively high (>5 mg Ni/m^3) (ICNCM, 1990; Grimsrud *et al.*, 2000). At various stages in this process, nickel-copper oxides may have been formed. In contrast, no excess respiratory cancer risks have been observed in workers exposed to lower levels (<2 Ni/m^3) of oxidic nickel free of copper during the refining of lateritic ores or in the nickel-using industry.

Specific operations where oxidic nickel was present and showed evidence of excess respiratory cancer risk include refineries in Kristiansand, Norway, Clydach, Wales, and Copper Cliff and Port Colborne, Ontario, Canada. In all instances, workers were exposed to various combinations of sulfidic, oxidic, and soluble nickel compounds. Nevertheless, conclusions regarding the carcinogenic potential of oxidic nickel compounds have been gleaned by examining those workers predominantly exposed to oxidic nickel.

In the case of Kristiansand, this has been done by examining workers in the roasting, smelting and calcining department (ICNCM, 1990) and by examining all workers by cumulative exposure to oxidic nickel (ICNCM, 1990; Andersen *et al.*, 1996). In the overall cohort, there was evidence to suggest that long-term exposure (≥15 years) to oxidic nickel (mainly nickel-copper oxides at concentrations of 5 mg Ni/m^3 or higher) was related to an excess of lung cancer. There was also some evidence that exposure to soluble nickel played a role in increasing cancer risks in these workers (see Section 5.3). The effect of cigarette smoking has also been examined in these workers (Andersen *et al.*, 1996; Grimsrud, 2001), with Andersen *et al.*, 1996 showing a multiplicative effect (*i.e.,* interaction) between cigarette smoking and exposure to nickel. Evidence of excess nasal cancers in this group of workers has been confined to those employed prior to 1955. This evidence suggests that oxidic nickel has been a stronger hazard for nasal cancer than soluble nickel, as 12 cases (0.27 expected) out of 32 occurred among workers exposed mostly to nickel oxides.

In the Welsh and Canadian refineries, workers exposed to some of the highest levels (10 mg Ni/m^3 or higher) of oxidic nickel included those working in the linear calciners and copper and nickel plants (Wales) and those involved in sintering operations in Canada. In Wales, oxidic nickel exposures were mainly to nickel-copper oxides or impure nickel oxide; in Canada, exposures were mainly to high-temperature nickel oxide with lesser exposure to nickel-copper oxides. Unfortunately, in the latter case, oxidic exposures were completely confounded by sulfidic nickel exposures, making it difficult to distinguish be-

tween the effects caused by these two species of nickel. Both excess lung and nasal cancer risks were seen in the Welsh and Canadian workers (Peto *et al.*, 1984; Roberts *et al.*, 1989a; ICNCM, 1990).

In contrast to the above refinery studies, studies of workers mining and smelting lateritic ores (where oxidic nickel exposures would have been primarily to silicate oxides and complex nickel oxides free of copper) have shown no evidence of nickel-related respiratory cancer risks. Studies by Goldberg *et al.* (1987; 1992) of smelter workers in New Caledonia showed no evidence of increased risk of lung or nasal cancer at estimated exposures of 2 mg Ni/m^3 or less. Likewise, in another study of smelter workers in Oregon there was no evidence of excess nasal cancers (Cooper and Wong, 1981; ICNCM, 1990). While there were excess lung cancers, these occurred only in short-term workers, not long-term workers. Hence, there was no evidence to suggest that the lung cancers observed were related to the low concentrations (≤1 mg Ni/m^3) of oxidic nickel to which the men were exposed (ICNCM, 1990).

In nickel-using industries, the evidence for respiratory cancers has also largely been negative. As noted in previous sections (Sections 5.1 and 5.2), most studies on stainless steel and nickel alloy workers that would have experienced some level of exposure to oxidic nickel have shown no significant nickel-related excess risks of respiratory cancer (Polednak, 1981; Cox *et al.*, 1981; Cornell, 1984; Moulin *et al.,* 1993, 2000; Svensson *et al.,* 1989; Simonato *et al.*, 1991; Gerin *et al.*, 1993; Hansen *et al.*, 1996; Jakobsson *et al.,* 1997; Arena *et al.,* 1998). In Swedish nickel-cadmium battery workers, there is some evidence of an increased incidence of nasal cancers, but it is not clear whether this is due to exposure to nickel hydroxide, cadmium oxide, or a combination of both (Jărup *et al*, 1998). In addition, little is known about the previous employment history of these workers. It is, therefore, not clear whether past exposures to other potential nasal carcinogens may have contributed to the nasal cancers observed in these workers. In contrast, no nickel-related increased risk for lung cancer has been found in these or other nickel-cadmium battery workers (Kjellström *et al,* 1979; Sorahan and Waterhouse, 1983; Andersson *et al.,* 1984; Sorahan, 1987; Jărup *et al.*, 1998).

From the overall epidemiological evidence, it is possible to speculate that the composition of oxidic nickel associated with an increase of lung or nasal cancer may primarily be nickel-copper oxides produced during the roasting and electrorefining of sulfidic nickel-copper mattes. However, careful scrutiny of the human data also reveals that high respiratory cancer risks occurred in sintering operations – where exposures to nickel-copper oxides would have been relatively low – and, possibly, in nickel-cadmium battery workers, where oxidic exposures would predominantly have been to nickel hydroxide. In addition to the type of oxidic nickel, the level to which nickel workers were exposed must also be taken into consideration. Concentrations of oxidic nickel in the high-risk cohorts (those in Wales, Norway, and Port Colborne and Copper Cliff, Canada) were considerably higher than those found in New Caledonia, Oregon, and most nickel-using industries. In the case of the nickel-cadmium battery workers, the early exposures that would have been critical to the induction of nasal cancers of long latency were believed to have been relatively high (>2 mg Ni/m^3). Hence, it may be that there are two variable – the physicochemical nature of the oxide and

the exposure level – that contribute to the differences seen among the various cohorts studied.

Animal data shed some light on the matter. In the previously mentioned NTP studies, nickel oxide was administered to rats and mice in a two-year carcinogenicity bioassay (NTP, 1996c). The nickel oxide used was a green, high-temperature nickel oxide calcined at 1,350°C; it was administered to both rats and mice for 6 hours/day, 5 days/week for 2 years. Rats were exposed to concentrations of 0, 0.5, 1.0, or 2.0 mg Ni/m^3. These concentrations are equivalent to over 5.0 to 20 mg Ni/m^3 workplace aerosol after adjusting for particle size differences and animal to human extrapolation (Hsieh *et al.,* 1999; Yu *et al.,* 2001). After two years, no increased incidence of tumors was observed at the lowest exposure level in rats. At the intermediate and high concentrations, 12 out of 106 rats and 9 out of 106 rats, respectively, were diagnosed with either adenomas or carcinomas. On the basis of these results, the NTP concluded that there was some evidence of carcinogenic activity in rats. In contrast, there was no evidence of treatment-related tumors in male mice at any of the doses administered (1.0, 2.0 and 4.0 mg Ni/m^3) and only equivocal evidence in female mice exposed to 1.0 but not 2.0 or 4.0 mg Ni/m^3.

Carcinogenic evidence for other oxidic nickel compounds comes from animal studies using routes of exposure that are not necessarily relevant to man (*i.e.*,intratracheal instillation, injection). In these studies, nickel-copper oxides appear to be as potent as nickel subsulfide in inducing tumors at injection sites (Sunderman *et al.*, 1990). There is, however, no strong evidence to indicate that black (low temperature) and green (high temperature) nickel oxides differ substantially with regard to tumor-producing potency. Some forms of both green and black nickel oxide produce carcinogenic responses, while other forms have tested negative in injection and intratracheal studies (Kasprzak *et al.*, 1983; Sunderman, 1984; Sunderman *et al.*, 1984; Berry *et al.*, 1985; Pott *et al.*, 1987, 1992; Judde *et al.*, 1987; Sunderman *et al.*, 1990).

On the whole, comparisons between human and animal data suggest that certain oxidic nickel compounds at high concentrations may increase respiratory cancer risks and that these risks are not necessarily confined to nickel-copper oxides. However, there is no single unifying physical characteristic that differentiates oxidic nickel compounds with respect to biological reactivity or carcinogenic potential. Some general physical characteristics which may be related to carcinogenicity include: particle size ≤5 µm, a relatively large particle surface area, presence of metallic or other impurities and/or amount of Ni (III). Phagocytosis appears to be a necessary, but not sufficient condition for carcinogenesis. Solubility in biological fluids will also affect how much nickel ion is delivered to target sites (*i.e.,* cell nucleus) (Oller *et al.*, 1997). The ability of particles to generate oxygen radicals may also contribute to their carcinogenic potential (Kawanishi *et al.,* 2001).

With respect to non-malignant respiratory effects, oxidic nickel compounds do not appear to be respiratory sensitizers. Based upon numerous epidemiological studies of nickel-producing workers, nickel alloy workers, and stainless steel workers, there is little indication that exposure to oxidic nickel results in excess mortality from chronic respiratory disease (Polednak, 1981; Cox *et al.*, 1981; Enterline and Marsh, 1982; Roberts *et al.*, 1989b; Simonato *et al.*, 1991; Moulin *et al.,* 1993, 2000; Arena *et al.,* 1998). In the few instances where excess risks of non-malignant

respiratory disease did appear-for example, in refining workers in Wales-the excesses were seen only in workers with high nickel exposures (>10 mg Ni/m^3), in areas that were reported to be very dusty. With the elimination of these dusty conditions, the risk that existed in these areas seems largely to have disappeared by the 1930s (Peto *et al.*, 1984).

In a study using radiographs of nickel sinter plant workers exposed to very high levels of oxidic and sulfidic nickel compounds (up to 100 mg Ni/m^3), no evidence that oxidic or sulfidic nickel dusts caused a significant fibrotic response in workers was reported (Muir *et al.*, 1993). In a recent study of Norwegian nickel refinery workers, an increased risk of pulmonary fibrosis was found in workers with cumulative exposure to sulfidic and soluble, but not oxidic nickel (Berge and Skyberg, 2001). The previously mentioned Kilburn *et al.* (1990) and Sobaszek *et al.* (2000) studies (see Section 5.1.1) showed mixed evidence of chronic effects on pulmonary function in stainless steel welders. Broder *et al.* (1989) showed no differences in pulmonary function of nickel smelter workers versus controls in workers examined for short periods of time (1 week); however, there were some indicators of a healthy worker effect in this cohort which may have resulted in the negative findings. Anosmia (loss of smell) has been reported in nickel-cadmium battery workers, but most researchers attribute this to cadmium toxicity (Sunderman, 2001).

Animal studies have shown various effects on the lung following relatively short periods of exposure to high levels of nickel oxide aerosols (Bingham *et al.*, 1972; Murthy *et al.*, 1983; Dunnick *et al.*, 1988; Benson *et al.*, 1989; Dunnick *et al.*, 1989). Effects have included increases in lung weights, increases in alveolar macrophages, fibrosis, and enzymatic changes in alveolar macrophages and lavage fluid. Studies of repeated inhalation exposures to nickel oxide (ranging from two to six months) have shown that exposure to nickel oxide may impair particle lung clearance (Benson *et al.*, 1995; Oberdörster *et al.*, 1995). Chronic exposures to a high-temperature nickel oxide resulted in statistically significant inflammatory changes in lungs of rats and mice at 0.5 mg Ni/m^3 and 1.0 mg Ni/m^3, respectively (NTP, 1996c). These values correspond to workplace exposures above 5-10 mg Ni/m^3. At present, the significance of impaired clearance seen in nickel oxide-exposed rats and its relationship to carcinogenicity is unclear (Oller *et al.*, 1997).

5.5 Sulfidic Nickel

Data relevant to characterizing the adverse health effects of nickel "sulfides" in humans arises almost exclusively from processes in the refining of nickel. Exposures in the refining sector should not be confused with those in mining, where the predominant mineral from sulfidic ores is pentlandite [$(Ni, Fe)_9S_8$]. Pentlandite is very different from the nickel subsulfides and sulfides found in refining. Although a modest lung cancer excess has been found in some miners (ICNCM, 1990), this excess has been consistent with that observed for other hard-rock miners of non-nickel ores (Muller *et al.*, 1983). This, coupled with the fact that millers have not presented with statistically significant excess respiratory cancer risks, suggests that the lung cancer seen in miners is not nickel-related (ICNCM, 1990). Further, pentlandite has not been shown to be carcinogenic in rodents intratracheally instilled with the mineral over their lifetimes (Muhle *et al.*, 1992). Therefore, for purposes of this document, it should be understood that any critical health effects discussed relative to

"sulfidic nickel" pertains mainly to nickel sulfides (NiS) and subsulfide (Ni_3S_2).

As in the case of oxidic nickel, it is the inhalation of sulfidic nickel compounds that is the route of exposure of greatest concern in occupational settings. No relevant studies of dermal exposure have been conducted on workers exposed to sulfidic nickel. Because exposures to sulfidic and oxidic nickel compounds have often overlapped in refinery studies, it has sometimes been difficult to separate the effects of these two nickel species from each other. Overwhelming evidence of carcinogenicity from animal studies, however, has resulted in the consistent classification of sulfidic nickel as a "known carcinogen" by many scientific bodies (IARC, 1990; ACGIH, 1998; NTP, 1998). This evidence is discussed below.

5.5.1 Inhalation Exposure: Sulfidic Nickel

The evidence for the carcinogenicity of sulfidic compounds lies mainly in sinter workers from Canada. These workers were believed to have been exposed to some of the highest concentrations of nickel subsulfide (15-35 mg Ni/m^3) found in the producing industry. They exhibited both excess lung and nasal cancers (Roberts *et al.*, 1989a; ICNCM, 1990). Unfortunately, as noted in Section 5.4, these workers were also concomitantly exposed to high levels of oxidic nickel as well, making it difficult to distinguish between the effects caused by these two species of nickel.

Further evidence for the respiratory effects of sulfidic nickel can be gleaned from nickel refinery workers in Clydach, Wales. Specifically, workers involved in cleaning a nickel plant were exposed to some of the highest concentrations of sulfidic nickel at the refinery (18 mg Ni/m^3) and demonstrated a high incidence of lung cancer after 15 years or more since their first exposure to cleaning. Analysis by cumulative exposure showed that Clydach workers with high cumulative exposures to sulfidic nickel and low level exposures to oxidic and soluble nickel exhibited higher lung cancer risks than workers who had low cumulative exposures to all three nickel species combined (ICNCM, 1990). Somewhat perplexing, however, was that the risk of developing lung or nasal cancer in this cohort was found primarily in those employed prior to 1930, although estimated levels of exposure to sulfidic nickel were not significantly reduced until 1937. This suggests that other factors (*e.g.,* possible presence of arsenic in sulfuric acid that resulted in contaminated mattes) could have contributed to the cancer risk seen in these early workers (Duffus, 1996). In another cohort of refinery workers in Norway, increased cumulative exposures to sulfidic nickel did not appear to be related to lung cancer risk, although workers in this latter cohort were not believed to be exposed to concentrations of sulfidic nickel greater than about 2 mg Ni/m^3 (ICNCM, 1990).

Because of the difficulty in separating the effects of sulfidic versus oxidic nickel in human studies, researchers have often turned to animal data for further guidance. Here, the data unequivocally point to nickel subsulfide as being carcinogenic. In the chronic inhalation bioassay conducted by the NTP (1996a), rats and mice were exposed for two years to nickel subsulfide at concentrations as low as 0.11 and 0.44 mg Ni/m^3, respectively. These concentrations correspond to approximately 1.1-4.4 mg Ni/m^3 workplace aerosol after accounting for particle size differences and animal-to-human extrapolation (Hsieh *et al.,* 1999; Yu *et al.,* 2001). After two years of expo-

sure, there was clear evidence of carcinogenic activity in male and female rats, with a dose-dependent increase in lung tumor response. No evidence of carcinogenic activity was detected in male or female mice; no nasal tumors were detected in rats or mice, but various non-malignant lung effects were seen. This study was in agreement with an earlier inhalation study which also showed evidence of carcinogenic activity in rats administered nickel subsulfide (Ottolenghi *et al.*, 1974). These studies, in conjunction with numerous other studies on nickel subsulfide (although, not all conducted by relevant routes of exposure) show nickel subsulfide to be a potent inducer of tumors in animals (NTP, 1996a).

With respect to non-carcinogenic respiratory effects, a number of animal studies have reported on the inflammatory effects of nickel subsulfide on the lung (Benson *et al.*, 1986; Benson *et al.*, 1987; Dunnick *et al.*, 1988, 1989; Benson *et al.*, 1989; NTP 1996a). These have been to both short- and long-term exposures and have included effects such as increased enzymes in lavage fluid, chronic active inflammation, focal alveolar epithelial hyperplasia, macrophage hyperplasia and fibrosis. For sulfidic nickel, the levels at which inflammatory effects in rats are seen are lower than for oxidic nickel, and similar to those required to see effects with nickel sulfate hexahydrate.

The evidence for non-malignant respiratory effects in workers exposed to sulfidic nickel has been mixed. Mortality due to non-malignant respiratory disease has not been observed in Canadian sinter workers (Roberts *et al.*, 1989b). This is in agreement with the radiographic study by Muir *et al.* (1993) that showed that sinter plant workers exposed to very high levels of oxidic and sulfidic nickel compounds did not exhibit significant fibrotic responses in their lungs. In contrast (as noted in Section 5.4), excess risks of non-malignant respiratory disease did appear in refining workers in Wales with high nickel exposures to insoluble nickel (>10 mg Ni/m^3). With the elimination of the very dusty conditions that likely brought about such effects, the risk of respiratory disease disappeared by the 1930s in this cohort (Peto *et al.*, 1984). In a recent study of Norwegian nickel refinery workers, an increased risk of pulmonary fibrosis was found in workers with cumulative exposure to sulfidic and soluble nickel (Berge and Skyberg, 2001). Increased odds ratios were seen at lower cumulative exposures of sulfidic than of soluble nickel compounds.

The mechanism for the carcinogenicity of sulfidic nickel (as well as other nickel compounds) has been discussed by a number of researchers (Costa, 1991; Oller *et al.*, 1997; Haber *et al.*, 2000a). Relative to other nickel compounds, nickel subsulfide may be the most efficient at inducing the heritable changes needed for the cancer process. *In vitro*, sulfidic nickel compounds have shown a relatively high efficiency at inducing genotoxic effects such as chromosomal aberrations and cell transformation as well as epigenetic effects such as increases in DNA methylation (Costa *et al.,* 2001). *In vivo*, nickel subsulfide is likely to be readily endocytized and dissolved by the target cells resulting in efficient delivery of nickel (II) to the target site within the cell nucleus (Costa and Mollenhauer, 1980a; Abbracchio *et al.*, 1982). In addition, nickel subsulfide has relatively high solubility in biological fluids which could result in the release of the nickel (II) ion resulting in cell toxicity and inflammation. Chronic cell toxicity and inflammation may lead to a proliferation of target cells. Since nickel subsulfide is the nickel compound most likely to induce heritable changes

in target cells, proliferation of cells that have been altered by nickel subsulfide may be the mechanism behind the observed carcinogenic effects (Oller *et al.*, 1997).

Because of these effects, sulfidic nickel compounds appear to present the highest respiratory carcinogenic potential relative to other nickel compounds. The clear evidence of respiratory carcinogenicity in animals administered nickel subsulfide by inhalation, together with mechanistic considerations, indicate that the association of exposures to sulfidic nickel and lung and nasal cancer in humans is likely to be causal (Oller, 2001).

5.6 Nickel Carbonyl

Unlike other nickel species, nickel tetracarbonyl (commonly referred to as nickel carbonyl) can be found as a gas or as a volatile liquid. It is mainly found as an intermediate in the carbonyl process of refining. By virtue of its toxicokinetics, it is the one nickel compound for which short-term inhalation exposures are the most critical. With respect to dermal exposures, although biologically possible, absorption through the skin has not been demonstrated in humans, nor have any dermal studies on animals been conducted. The discussion, below, therefore, focuses on inhalation exposures.

5.6.1 Inhalation Exposure: Nickel Carbonyl

Nickel carbonyl delivers nickel atoms to the target organ (lung) in a manner that is probably different from that of other nickel species. After nickel carbonyl inhalation, removal of nickel from the lungs occurs by extensive absorption and clearance. The alveolar cells are covered by a phospholipid layer, and it is the lipid solubility of nickel carbonyl vapor that is of importance in its penetration of the alveolar membrane. Extensive absorption of nickel carbonyl after respiratory exposure has been demonstrated. Highest nickel tissue concentrations after inhalation of nickel carbonyl have been found in the lungs, with lower concentrations in the kidneys, liver, and brain. Urinary excretion of nickel increases in direct relationship to exposure to nickel carbonyl (Sunderman *et al.*, 1986).

Acute toxicity is of paramount importance in controlling risks associated with exposure to nickel carbonyl. The severe toxic effects of exposure to nickel carbonyl by inhalation have been recognized for many years. The clinical course of nickel carbonyl poisoning involves two stages. The initial stages are characterized by headache, chest pain, weakness, dizziness, nausea, irritability, and a metallic taste in the mouth (Morgan, 1992; Vuopala *et al.*, 1970; Sunderman and Kincaid, 1954). There is then generally a remission lasting 8-24 hours followed by a second phase characterized by a chemical pneumonitis but with evidence, in severe cases, of cerebral poisoning. Common clinical signs in severe cases include tachypnoea, cyanosis, tachycardia, and hyperemia of the throat (Shi, 1986). Hematological results include leukocytosis. Chest X-rays in some severe cases are consistent with pulmonary edema or pneumonitis, with elevation of the right hemidiaphragm. Shi reported three patients with ECG changes of toxic myocarditis.

The second stage reaches its greatest severity in about four days, but convalescence is often protracted. In ten patients with nickel carbonyl poi-

5. Toxicity Of Nickel Compounds

soning, there were initial changes in pulmonary function tests consistent with acute interstitial lung disease (Vuopala *et al.*, 1970). However, these results returned to normal after several months.

The mechanism of the toxic action of nickel carbonyl has never been adequately explained, and the literature on the topic is dated (Sunderman and Kincaid, 1954). Some researchers have held the view that nickel carbonyl passes through the pulmonary epithelium unchanged (Amor, 1932). However, as nickel carbonyl is known to be reactive to a wide variety of nitrogen and phosphorous compounds, as well as oxidizing agents, it is not unreasonable to assume that it is probably reactive with biological materials (Sunderman and Kincaid, 1954). It is known to inhibit the utilization of adenosine triphosphate (ATP) in liver cells and brain capillaries (Joo, 1969; Sunderman, 1971). Following acute exposure to nickel carbonyl, sections of lung and liver tissue have been shown to contain a granular, brownish-black, noniron-staining pigment (Sunderman *et al.*, 1959). It has not been established, however, whether these dark granules represent metallic nickel or the compound, itself. Sunderman *et al.* (1959) proposed that nickel carbonyl may dissociate in the lung to yield metallic nickel and carbon monoxide, each of which may act singly, or in combination with each other, to induce toxicity.

Evidence of chronic effects at levels of exposure below those which produce symptomatic acute toxicity is difficult to find. The only epidemiological study that investigated specifically the possible carcinogenic effect of nickel carbonyl (Morgan, 1992) was limited in power and confounding factors–such as exposures to certain oxidic and sulfidic nickel species–thereby clouding any interpretation regarding the contribution of nickel carbonyl, *per se*, to the carcinogenic risk.

In animals, as in humans, the lung is the primary target organ for exposure to nickel carbonyl regardless of route of administration, and the effects in animals are similar to those observed in humans. Experimental nickel carbonyl poisoning in animals has shown that the most severe pathological reactions are in the lungs with effects in brain and adrenal glands as well. Acute toxicity is of greatest concern. The LD_{50} in rats is 0.20 mg Ni/liter of air for 15 minutes or 0.12 mg/rat. Effects on the lung include severe pulmonary inflammation, alveolar cell hyperplasia and hypertrophy, and foci of adenomatous change.

With respect to carcinogenic effects, studies on the carcinogenicity of nickel carbonyl were performed prior to present day standardized testing protocols, but because of the extreme toxicity of this material, more recent studies are not likely to be conducted. Studies by Sunderman *et al.*, (1959) and Sunderman and Donnelly (1965) have linked nickel carbonyl to respiratory cancer, but high rates of early mortality in these studies preclude a definitive evaluation. It would be desirable to have additional studies with less toxic levels of exposure permitting a higher proportion of the animals to survive. This would provide a more complete understanding of the spectrum of lung pathology produced by nickel carbonyl. Nevertheless, the deficiencies in these early studies preclude reaching any definitive conclusions regarding the carcinogenicity of nickel carbonyl via inhalation. Possible developmental toxicity effects are also of concern for nickel carbonyl. In a series of studies, Sunderman *et al.* (1979, 1980) demonstrated that nickel carbonyl, administered by inhalation (160-300 mg Ni/m^3) or injection (before or a few days after implantation) produced various types of fetal malformations in hamsters and rats.

6. Assessing The Risks Of Workers Exposed To Nickel

Any efforts to evaluate occupational health risks such as those identified in Chapter 5 must start with good data collection. This includes not only monitoring workplace exposures (discussed in Chapter 7), but assessing the health of individual workers with the ultimate goal of keeping the worker healthy and reducing the overall risks in the work environment. It is not enough to monitor workers periodically, programs must be implemented in ways that allow for the systematic collection of data that can be used in epidemiological studies and, subsequently, risk assessment. In some countries, implementation of a health surveillance program is obligatory. In such instances, any company-based surveillance program should be in compliance with the relevant local/national guidelines. Developing infrastructure and systems that support consistent data collection and storage requires effort, careful planning, and an adequate allocation of resources. It means enlisting the total commitment and cooperation of the most senior members of the management team (starting with the CEO) to the most junior constituents of the labor force. A number of specific steps have been identified as being basic to setting up a data collection system for quantitative risk assessment (Verma et al., 1996; ICME, 1999[3]). These are discussed below, in a modified form, with particular reference to nickel where appropriate.

6.1 Determining The Population At Risk

A worker is "at risk" if he or she has a greater chance of developing disease than a similar, but non-exposed worker (Verma *et al.*, 1996). Using this broad based definition of an "at risk" worker, it is clear that not only production workers, but office workers and support staff may have occasion to be exposed to nickel and its compounds in various industrial settings. Consideration should also be given to contractors, such as temporary workers or long-term maintenance crews employed at factories, as some of these workers may be employed in potentially high exposure jobs. While the management and follow-up of contractors may not be the direct responsibility of a given nickel company, it may, nevertheless, be useful in some nickel operations to document contractors' exposures and maintain records. Hence, for purposes of risk assessment, records should be kept on most, if not all, workers employed in the nickel industry. Companies should assign a unique identifier to each individual. Use of last names and/or birth dates is not recommended, as such identifiers may be shared by more than one employee. Sequentially assigning numbers to workers at date of hire or devising alpha/numerical codes for each individual is preferred. Once assigned to a worker, a number should always refer to that individual only.

Identification information that should be recorded includes the employees' full name and that of his or her parents, birth date, gender, place of birth, ethnic origin, other significant dates (such as date of hire, date of departure, date of death, *etc.*) and other potentially identifying data (such as social security or medical insurance numbers). Records should be periodically updated (even after employees have retired or left for other employment); they should also be well maintained and easily retrievable (Verma *et al.*, 1996). Consideration should be given to creating coding that would be universal throughout the nickel industry so that meaningful epidemiological studies can be optimized (Hall, 2001). This would apply not only to identification data, but

[3] *The International Council on Metals and the Environment, now known as the International Council on Mining and Metals.*

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to any data collected as part of a health surveillance program (see below).

6.2 Identifying The Hazards

A hazard can be defined as the set of inherent properties of a substance that makes it capable of causing harm to humans (Cohrssen and Covello, 1989). The likelihood of harm resulting from exposures determines the risk. As noted in Chapter 5, under certain circumstances (*e.g.,* high exposures or prolonged contact) every nickel species may be capable of causing some type of harm[4]. It is therefore very important to identify all potentially harmful substances and to monitor and control exposures in order to manage the risk.

With respect to hazards, all the nickel species present in an industrial setting should be identified and a complete inventory made of raw materials used, materials produced, by-products and contaminants (Grosjean, 1994; Verma *et al.,* 1996; ICME, 1999). Consideration should be given to monitoring these materials not only under normal operations, but also when short-term peak exposures occur (*e.g.,* during maintenance). In addition, a record should be made of all procedures and equipment used (including control equipment such as local exhaust ventilation and respirators), changes in processes, and changes in feed materials. Preparing flow charts and floor plans can help to identify areas where potentially harmful substances might exist (Duffus, 1996; Verma *et al.,* 1996; ICME, 1999).

Complementing this description of the physical plant should be a description each of the worker's employment history. Such a work history should include both past and present employment (Hall, 2001). A past employment history should include:

- All previous workplaces.
- All previous workplace exposures (both qualitative and quantitative).
- Duration of all previous workplace assignments.
- Nature of work performed at all previous worksites.

Present employment records should include:

- Date of start of work assignments at present employment.
- Duration of all work assignments at present employment.
- Nature of work performed with each work assignment.
- Exact location of each work assignment performed.
- Details of exposure *(e.g.,* nickel-containing substances, dusts, noise). Measurements pertaining to the work assignment (particularly noting whether these measurements are based on static or personal sampling and how they were obtained (see Chapter 7 for further discussion).
- Health surveillance/biological monitoring records where appropriate (see Section 6.3 below).

Periodic updates of exposure data and job histories should be conducted on all workers.

[4] *The nickel "species" most relevant to the workplace are metallic nickel (including elemental nickel and nickel alloys), oxidic, sulfidic, and soluble nickel compounds, and nickel carbonyl.*

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6.3 Assessing Exposures And Health Outcomes

With respect to exposures, two types of exposure data are required: those that pertain to the ambient environment (*e.g.,* workplace air) and those that pertain to the internal environment of the worker (*e.g.,* health surveillance). To be of use in risk assessment, each must be linked to the other. Workplace surveillance (air monitoring) is discussed in detail in Chapter 7. Human health surveillance is discussed below.

Health surveillance may be used to evaluate an individual's health prior to, during, and at termination of employment. Occasionally, it also may be used during retirement. A properly executed health surveillance plan can be useful in determining changes in the health status of an employee. However, considerable clinical skill and judgment will be required to assess whether any change can be attributed to workplace conditions.

In countries where it is possible to obtain mortality or cancer registry data, follow-up of personnel who have left the industry is strongly recommended so that information on the eventual cause of death can be made available for possible epidemiological research. Likewise, employers are advised to retain copies of death certificates of all personnel who die while still employed or as pensioners. Special efforts to ascertain the vital status of workers who have "quit" the workforce are recommended (Verma *et al.*, 1996).

In addition to mortality data, morbidity data may also be obtained in certain countries as part of voluntary data collection programs, such as the United Kingdom's Occupational Physicians Reporting Activity (OPRA) program, or as part of a national, state, or provincial accident/disease registry or workers' compensation program. Such data may be useful in identifying occupational disease trends (*e.g.,* cases of occupational asthma) within an industry sector.

The decision to commence a surveillance program has many biological, social, and legal considerations that must be taken into account. As noted in the introduction, in some countries, implementation of a health surveillance program is obligatory. In such instances, advice should be sought from the relevant local/national authority. Further legal considerations may include requirements for medical recordkeeping. In some countries, medical records are required to be kept for the duration of a worker's employment plus an additional prescribed time (usually 30 to 40 years).

Issues such as the invasiveness, sensitivity, and accuracy of testing procedures should also be considered, and any potential health benefits of these procedures should be weighed against the risks of performing such tests. Where possible, tests should be designed to investigate the quantitative relationship between the ambient workplace exposure, the biological measurement of the exposure, and the health effect of concern. The rights of workers with respect to issues such as confidentiality and compulsory examination must be carefully considered. Any health data gathered and recorded should be subject to rigorous quality control. The International Council on Mining and Metals has developed a *Guide to Data Gathering Systems for the Risk Assessment of Metals* (ICME, 1999). Useful information regarding the data needs of a health surveillance program is provided within this guide.

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In structuring a health surveillance program, consideration ideally should be given to the components discussed below.

6.3.1 Pre-Placement Assessment

The purpose of any pre-placement examination is to fit the worker to the job and the job to the worker. The objective is to identify any pre-existing medical conditions that may be of importance in hiring and job-placement-either at the time of hire or in the instance of a job transfer-while taking care to consider local laws regarding discriminatory practices. This examination can also provide baseline data that can be used to measure functional, pathological, or physiological changes in workers over time, thus, facilitating future epidemiological studies related to heath effects. Of particular importance is the identification of pre-existing medical conditions in target organs that potentially might be affected by nickel and its compounds (notably the respiratory system and skin, but also reproductive and renal systems).

Procedures for pre-placement health examinations are well defined but may in practice vary from country to country and between industries and occupations. However, a pre-placement examination for nickel workers should ideally include:

- Baseline health data such as height, weight, and vital statistics.
- A detailed history of previous diseases and occupational exposures (see above). The focus should be on previous lung problems and previous or present exposure to lung toxins such as silica, asbestos, irritant gases, etc.
- A history of personal hobbies or activities that might involve exposures to potential toxicants, particularly those that might affect target organs of concern to nickel species (*e.g.,* furniture restoration in the case of the lung and possibly the skin, or woodworking in the case of nasal cancers).
- Past or present history of any allergies (particularly to nickel), including asthma.
- Identification of personal habits (smoking, hygiene, alcohol consumption, fingernail biting) that may be relevant to work with nickel, its compounds, and alloys. Histories should be sufficiently detailed. For example, for smoking, the type of smoking, duration, amount smoked, and age of onset of smoking should be recorded. Any exposure to second hand smoke should be noted.
- Complete physical examination with special attention to respiratory, dermal, and, possibly, renal problems. Validated dermal and respiratory questionnaires should be included. Renal function may need to be checked as the kidneys are the main route of excretion of absorbed nickel.
- Specific to women, reproductive questionnaires and/or examinations with special emphasis on pregnant or lactating female workers who may potentially be exposed to nickel carbonyl and or soluble nickel compounds.
- Evaluation of the individual to determine the appropriate respiratory equipment (if any) that may be worn.

In addition to the items listed above, there are a number of clinical tests that may be performed to characterize the baseline data more efficiently. These include:

- posterior/anterior chest X-ray,

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- lung function tests using classical spirometry (*e.g.,* FVC, FEV1.0),
- audiometric testing, and
- vision testing.

With respect to the latter two pre-placement tests, audiometric and visual acuity tests are commonplace where noise levels in certain facilities are high and where good vision is especially important. Reliability and accuracy are essential for the above tests to be useful. The chest X-ray should be done by a quality facility and the films themselves interpreted by a radiologist certified as a "B reader" according to the International Labour Organization. The pulmonary function tests should be administered by a certified technician who is competent in instructing individuals through the test procedure and in recognizing poor test performance (Hall, 2001).

It should be noted that none of these tests are specific to the nickel industry and that the necessity for conducting them may be job-dependent. For example, it may be important to establish the lung function of an applicant who has previously been exposed to high dust levels or for whom current job placement might involve production areas. Conversely, lung function and audiometric testing may not be necessary where employees are working in relatively non-dusty or quiet environments (*e.g.,* administrative offices).

Skin patch testing is not recommended as a routine pre-employment procedure because there is a possibility that such tests may sensitize the applicant. However, in special circumstances, such testing may be warranted for purposes of clinical diagnosis. In view of the danger of sensitization and the difficulty in interpreting test results, patch testing should only be undertaken by persons experienced in the use of the technique.

Testing for allergic nickel dermatitis, if deemed necessary by a physician, usually involves patch testing with either 2.5 or 5 percent nickel sulfate in petrolatum; however, there is some evidence that other vehicles, such as water, dimethylsulfoxide, and softisan may prove more sensitive (Lammintausta and Maibach, 1989). It should be noted that patch tests may be ambiguous with respect to characterizing a pre-existing sensitivity versus a primary irritation. Because of this, various *in vitro* tests have been proposed as alternatives to patch testing, including the lymphocyte transformation test (LTT) (McMillan and Burrows, 1989; Lammintausta and Maibach, 1989). However, as these tests have not been completely validated as yet, they are not recommended for use by the nickel industry at this time. A number of sampling protocols for dermal contamination studies have been advocated, but standardization remains a problem (Gawkrodger, 2001). Methods are needed to be able to measure the amounts of soluble nickel (the ultimate allergen) from particulate and total nickel separately. Currently, the most practical methods for collecting nickel from workers' skin and work surfaces are forensic tape and wet pads (Gawkrodger, 2001).

With respect to biological monitoring, it should be noted from the outset that any biological monitoring program, while useful in some situations, may be of limited utility in others (see Section 6.3.3). Nevertheless, should a facility decide to undertake a biological monitoring program, it might be useful to establish baseline nickel concentrations in urine and/or serum as part of the pre-placement program (see Section 6.3.3 for further details on sampling).

In conclusion, it should be stressed that plant physicians will have to establish their own criteria

on which to accept or reject an applicant for job placement depending upon the requirements of the job and the applicant's suitability. Careful consideration must be given to local laws regarding discriminatory practices. Special consideration should be given to the placement of personnel with past or present contact dermatitis or respiratory disease (especially asthma) in jobs where physical demands may be high, where there is a risk of significant nickel exposure, or where respiratory protection may have to be worn. In the case of applicants with past histories of nickel allergy, care should be taken to find suitable employment where contact with nickel-containing items will neither be direct nor prolonged and the risks of promoting a recurrence are negligible (Fischer, 1989).

6.3.2 Periodic Assessment

The purpose of a periodic assessment is to monitor the general health of the worker at established times during the course of employment. Periodic examinations may be undertaken for three distinct purposes:

- To evaluate the general health status and lifestyle of an employee as part of a non-specific employment package.
- To assess the health status of an employee with respect to a specific industry or operation within an industry.
- To provide ongoing health surveillance of workers for use in epidemiological studies.

Before undertaking any such specific program, the occupational health physician should carefully consider:

- The needs and objectives of the program.
- The usefulness of the possible or planned procedures in indicating current disease or forecasting future significant pathological change.
- The potential benefits to both the individual and the employer.
- Existing legal requirements to monitor workers periodically and ensure that any program implemented by a company is in compliance with local/national regulations.

At the outset, a procedure should be agreed upon by both management and the employees' representatives on the action to be taken with respect to those individuals who are found to have problems that render them unsuitable for their current work (*e.g.,* a worker presenting with skin allergies). A single approach may not be applicable to all companies; hence, solutions may need to be tailored to meet the specific needs of a given company and its workers. Any actions taken to remedy a problem should consider the practical consequences of moving a worker, *e.g.,* financial repercussions and job prospects, as well as potential legal constraints such as medical removal provisions of applicable occupational health regulations.

As with pre-placement examinations, plant-specific periodic assessments should examine the general health and lifestyle of a worker, as well as nickel-associated concerns. Such examinations should include a reevaluation of personal habits and recent illnesses, standardized respiratory and dermal symptom questionnaires, a physical examination, and a reevaluation of the worker's ability to use the types of respiratory equipment that may be required for particular tasks. As noted in the beginning of this Chapter, air monitoring data (discussed further in Chapter 7) needs to be linked to health surveillance data; hence, any personal dust monitoring for nickel data

should be kept in the worker's medical records. Review of these records with the worker should be undertaken at the time that a periodic assessment is conducted.

X-rays and pulmonary function tests are surveillance tools of value to detect the presence of pulmonary abnormalities at a group level. Unless a risk assessment indicates otherwise, measurements of respiratory function and chest X-rays are recommended every five years for surveillance. Depending on the age of the workers (45 years or older), the smoking status, and the job task (nature, duration and level of dust/nickel exposure), more frequent chest X-rays may be appropriate. However, if abnormalities are detected, further tests should be carried out as appropriate, and the frequency of surveillance should be increased. It should be noted that in some countries chest X-rays may be required by law.

6.3.3 Biological Monitoring

For some metals, biological monitoring of urine, blood, and other tissues or fluids may provide a reasonable estimate of exposure which is predictive of health risks. This has not been shown to be the case for nickel (Sunderman *et al.*, 1986). While urinary and blood nickel levels provide a reasonable estimate of recent exposure to soluble nickel compounds and fine nickel metal powders, they do not provide a reliable measure of exposure to other less soluble forms of nickel, nor do they truly provide a reliable measure of total body burden. Rather, they provide an integrative measure of the nickel that has been absorbed in the body from all routes of exposure (inhalation, dermal, and oral). Furthermore, with the exception of nickel carbonyl gas (see below), no consistent correlation has been found between nickel concentrations in biological media and increased health risks following exposure to either soluble or insoluble nickel compounds. Assessments of workplace exposure to inhalable aerosols are likely to reflect health risks better than consideration of nickel levels in urine or plasma (Werner *et al.*, 1999). Hence, for the most part, of blood and urinary nickel concentrations are not recommended as surrogates of nickel exposure or nickel-associated health risk.

That said, biological monitoring does provide additional exposure information on an individual and group basis, and also an assessment of the effectiveness of control measures to protect the worker. It can provide reassurance to workers that control measures do work and that they are not absorbing an excessive amount of a potentially harmful substance from the workplace (White, 2001). It can also be used as an education tool for good personal hygiene. It is mainly useful in situations where exposures are to soluble nickel compounds, nickel metal powder, or nickel carbonyl. It is less useful in situations where exposures are predominantly to water insoluble compounds or where exposures are mixed.

Three factors are key to a successful biological monitoring strategy (White, 2001). They are:

- Appropriate Sampling – correct sample type, proper sample timing of sample collection, and avoidance of contamination.
- Accuracy of Measurement – use of validated methods of analysis and quality assurance procedures.
- Interpretation of Results – knowledge of the chemical and physical characteristics of the substance, routes of exposure and uptake, metabolism and excretion and biological limit values.

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If a biological monitoring program is implemented, it should augment an environmental monitoring program, so that the biological monitoring information alone is not used as a surrogate of exposure. Both programs should be implemented in conjunction with an industrial hygiene program. In the past, health-based limits of permissible nickel concentrations in blood or urine[5] of individuals or groups of workers exposed in either the using or producing industries were lacking due to a paucity of quantitative information on dose-response relationships between these parameters and nickel toxicity (Sunderman et al., 1986). However, some regulatory bodies are now attempting to set Biological Limit Values (BLVs) for nickel and nickel compounds in conjunction with Occupational Exposure Limits (OELs), despite the fact that the utility of setting BLVs for nickel has been questioned by some (Werner et al., 1999). Both OELs and BLVs are discussed in more detail in Chapter 9. It is worth noting that there are no established guidelines for how frequently one should monitor workers, although preliminary recommendations are made below.

6.3.3.1 Nickel in Urine

Soluble nickel compounds are rapidly excreted from the body; consequently, they do not bioaccumulate (Hall, 1989). The biological half-time of soluble nickel in urine following inhalation has been reported to range from 17 to 39 hours in humans (Tossavainen *et al.*, 1980). Reported urinary excretion of nickel following oral exposures is also quite rapid (Sunderman *et al.*, 1989). Because of this rapid clearance of soluble nickel from the body, regardless of route of exposure, levels in urine are indicative only of relatively recent exposures.

Relatively insoluble nickel, on the other hand, is known to accumulate in tissue such as lung, where, depending upon particle size, it may only slowly be absorbed over time. Nickel in urine, therefore, only reflects the fraction of insoluble nickel that has been absorbed. The smaller the particle, the more likely it is to be rapidly absorbed and excreted. This phenomenon may account for the relatively short half-times of nickel in urine, ranging from 30 to 53 hours, reported by Zober *et al.* (1984) and Raithel *et al.* (1982) for workers exposed to welding fumes and/or insoluble nickel particles of small diameter. Conversely, some have suggested that for workers presumably exposed to insoluble nickel of larger particle size, the biological half-time of stored nickel may be considerably longer, possibly ranging from months to years (Torjussen and Andersen, 1979; Boysen *et al.*, 1984; Morgan and Rouge, 1984).

Urine samples for nickel analysis can be collected by spot sampling or by 24-hour sampling. The most sensitive method for correlating urinary nickel concentrations to air nickel concentrations is the 24-hour urine sample (Hall, 1989). A spot urinary sample tends to be more variable and, therefore, is not as informative. However, since collection of a 24-hour urine sample may be impractical in an occupational setting, post-shift or end-of-week spot sampling is the preferred method when 24-hour sampling cannot be carried out.

Due to variable urine dilution, spot samples are typically normalized on the basis of either creati-

[5] *Some attempts have been made to look at nickel in nasal tissue as a possible indicator of nickel exposure (Torjussen et al., 1979; Boysen et al., 1982). However, due to the problems associated with the invasiveness of the biopsy technique, the use of nasal tissue monitoring is not recommended as a routine procedure (Aitio, 1984).*

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nine concentration or specific gravity. A study of 26 electrolytic nickel refinery workers suggests that specific gravity normalization of nickel concentration is more appropriate than creatinine adjustment (Sanford *et al.,* 1988). However, drawbacks to both methods exist, depending upon factors such as the degree of dilution of the sample, the fluctuations of salt in the body, and the presence of glycosuria or proteinuria (Lauwerys and Hoet, 1993). Some evidence exists that on a group basis, there may be no difference between corrected and uncorrected samples (Morgan and Rouge, 1984). A recent study of Scandinavian nickel workers, however, suggests that corrected urinary samples (adjusted for creatinine concentrations) correlate better with measurements of nickel aerosol than do "raw" uncorrected samples (Werner *et al.*, 1999). A study of urinary nickel levels at a nickel refinery in Russia showed lower urinary nickel values in females than in male workers with similar inhalation exposures (Thomassen *et al.,* 1999).

It is important that urine samples be analyzed by a reputable laboratory accustomed to doing the required analyses (Hall, 2001). It is also important that the analyses be reported in appropriate units; in the case of urine, typically as mg Ni/gm creatinine or µmol Ni/mol creatinine. If a biological monitoring program is instituted, urine nickel samples should be collected quarterly or semi-annually (Hall, 2001).

Urinary nickel levels can vary considerably, even in non-occupationally exposed individuals. Because of this, they are of most use when interpreted on a group basis. Reported urinary nickel concentrations in non-exposed individuals range from approximately 0.2 to 10 µg Ni/L, depending upon the method of analysis (Sunderman *et al.*, 1986; Sunderman, 1989).

As noted above, the only nickel compound for which a correlation between urinary nickel concentrations and adverse health effects has been found is nickel carbonyl. There is a close correlation between the clinical severity of acute nickel carbonyl poisoning and urinary concentrations of nickel during the initial three days after exposure (Sunderman and Sunderman, 1958). The correlations are as follows:

- Mild Symptoms: 60 to 100 µg Ni/l (18-hour urine specimen).
- Moderate Symptoms: 100 to 500 µg Ni/l (18-hour urine specimen).
- Severe Symptoms: >500 µg Ni/l (18-hour urine specimen).

These values are only relevant, however, where urinary nickel is not elevated due to other exposures.

Recent experience at a nickel carbonyl refinery from 1992 to 2002 has shown that the clinical severity of the acute nickel carbonyl exposure can also be correlated to nickel levels in early urinary samples (within the first 12 hours of exposure). The use of an 8-hour post exposure urinary nickel specimen may also be helpful in categorizing cases and determining the need for chelation therapy. Of 170 potentially exposed cases, mild cases were defined as having <150 µg Ni/l, moderate cases as having 150-500 µg Ni/l, and severe cases as having >500 µg Ni/l (with 8 hours post exposure samples) (Dr. S. Williams, Inco, personal communication). Chelation therapy with disulfiram was considered with respect to the moderate and severe groups only.

Nickel carbonyl is also the only nickel compound for which information is available regarding treatment following acute exposure. The administra-

tion of either sodium diethyldithiocarbamate (Dithiocarb) or its analogue, tetraethylthiuram disulfide (Disulfiram, which is marketed as the proprietary drug, Antabuse, and is more readily commercially available), has been recommended in the treatment of nickel carbonyl poisoning. Both agents work by chelating the metal in the blood and transporting it to the kidneys for rapid excretion in urine.

In summary, from the above discussions, it is evident that there are both advantages and disadvantages to using urinary nickel concentrations in biological monitoring programs. The disadvantages include fluctuating specific gravity, problems associated with dilute urine, matrix variability and possible dust contamination, and, with the exception of nickel carbonyl, the lack of any dose-effect relationship (Sunderman, 1989). The advantages are the non-invasiveness of the technique and convenience of collection. Also, urinary nickel concentrations are higher than concentrations in other biological media, improving sensitivity, analytical accuracy, and precision (Sunderman *et al.*, 1986). When compared to other methods for estimating biological exposures (*e.g.,* serum nickel), the advantages of collecting urinary nickel make it the preferred biological monitoring method.

6.3.3.2 Nickel in Blood

The half-time of nickel in serum is similar to that in urine. Values ranging from 20 to 34 hours have been reported for workers exposed to soluble nickel compounds via inhalation (Tossavainen *et al.*, 1980). A half-time of 11 hours was observed in human volunteers orally dosed with soluble nickel sulfate hexahydrate (Christensen and Lagesson, 1981).

Just as in the case of urinary nickel, serum nickel levels cannot be used as indicators of specific health risks. They are of most use when interpreted on a group basis. Serum or plasma nickel levels can provide an indication of recent exposure to nickel metal powder or relatively soluble nickel compounds. Likewise, elevated serum or plasma nickel levels in individuals exposed solely to less soluble nickel compounds may reflect significant absorption that could be indicative of a corresponding long-term increase in workplace exposures. Normal serum or plasma nickel values in workers exposed to less soluble forms of nickel do not necessarily indicate an absence of exposure to such forms. Because serum nickel is not a good predictor of health risks, conclusions regarding the presence or absence of risk should not be drawn from such data.

Serum and plasma concentrations of nickel tend to be similar, whereas whole blood concentrations have been found to be approximately twice that of serum and plasma (Baselt, 1980). Pre- or post-shift sampling is typically performed (Sunderman *et al.*, 1986), although in some instances, both morning and after-work samples have been taken in the same workers (Høgetveit *et al.*, 1980). Nickel concentrations in the serum and plasma of healthy non-exposed individuals range from 0.05 to 1.1 µg Ni/L (Sunderman *et al.*, 1986). Like urine nickel samples, it is important that blood samples be analyzed by a reputable laboratory. Analysis should be reported as mg Ni/100ml or µmol Ni/100ml. If a biological monitoring program is instituted, blood nickel samples should be collected annually (Hall, 2001).

As with urinary nickel measurements, there are both advantages and disadvantages to using serum nickel concentrations in biological monitor-

ing programs. The primary disadvantages of measuring serum or plasma nickel levels are that the sampling technique is invasive and serum and plasma nickel levels are lower than urinary levels (Sunderman, 1989). The primary advantages are that serum and plasma samples are less subject to matrix variability fluctuations and to contamination from workplace dust.

6.4 Developing Data Collection And Management Systems

An integral part of setting up a data collection system for quantitative risk assessment is selecting and/or designing an appropriate software program for database management. Given the volume of data required to assess the risks of workers (exposure data, surveillance and screening data, biological monitoring, etc.), it is imperative that some form of automated data collection system be implemented. Often the problem of assessing risks is not so much the absence of relevant data as it is its inaccessibility and lack of quality assurance in the data that exists (Lippmann, 1995). Whether the system used is commercial or specifically designed by company personnel, it should embody the following features (Verma *et al.*, 1996; ICME, 1999):

- Compatibility with other computer databases in the company (*e.g.,* payroll or health benefits).
- Use of unique identifiers as the key field for all employee-based files.
- Development of a centralized database that can summarize and link all individual records.
- Quality assurance programs to check data quality and integrity.
- Built-in mechanisms for protecting the confidentiality of employees' personal information.
- Fail-safe operations (*e.g.,* database replication) to prevent loss of information. Storage of hard copy computer records (although resource intensive) can provide an additional level of safety, ensuring that no data are lost (Duffus, 1996).

6.5 Training

It is preferable that any implemented health surveillance program be administered by qualified occupational health specialists. The expertise of professional industrial hygienists, physicians, and technicians will likely be required. However, once a proper data collection system is in place, non-expert staff can help to collect some of the data on a day-to-day basis. This is particularly true for much of the ambient monitoring data discussed in greater detail in Chapter 7. Workers can be trained to collect data "on the job" or through short-term courses. Training should include instruction in epidemiology, basic industrial hygiene, air sampling, and toxicology/health effects (Verma *et al.*, 1996). Good communication and teaching skills will be required of employees helping to administer health and workplace surveillance programs. Distance education courses are offered by several research centers and universities so that personnel from small companies or more remote locations need not be prohibited from acquiring the necessary skills required to collect useful data for risk assessment purposes. Sources for training personnel are provided in the aforementioned *Guide to Data Gathering Systems for the Risk Assessment of Metals* (ICME, 1999).

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6.6 Benchmarking

It is important that any surveillance program implemented be evaluated to determine how well it is working. This is an often overlooked feature of data collection. A data gathering system is not a static system. Improved technology, altered plant processes, and changes in staff can all affect the type of data collected and the way they are collected (ICME, 1999). Benchmarking provides a means to integrate such changes and to improve the efficiency of established programs. It is simple in concept, requiring the assessment of the strengths and weaknesses of any data gathering system within a company and acting to implement changes where and when weaknesses are identified.

Evaluations made should be both "top-down" and "bottom-up". It is not enough for management, alone, to evaluate the effectiveness of a program:

- the opinions and suggestions of workers on how to improve health and workplace surveillance programs should also be sought;
- data gaps need to be identified;
- goals need to be set against which future evaluations can be made;
- action plans for making changes to any deficient processes need to be drafted; and
- feasibility, including financial and staff resources, needs to be considered.

In summary, it is important not only to gather data, but to use the data in a way that identifies and reduces the risks of occupational exposures in the workplace so that they are acceptable from the perspectives of health, safety and the environment.