

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,

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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, lim-

itless. 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 ($>10 \text{ mg Ni/m}^3$) 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)

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are much lower, with current measurements generally averaging <1 mg Ni/m³. 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/m³.

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/m³) 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.

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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, in-

cluding 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/m³, 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-

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sure to total nickel was extremely high (382 mg Ni/m³). 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 me-

tallic 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/cm²/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/cm²/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.

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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/m³. However, a few recent studies have noted that exposures slightly lower than this (around 0.5 mg Ni/m³) 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/m³ did not show any evidence of carcinogenicity. However, at workplace equivalent levels above 0.1 mg Ni/m³, 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 evi-

dence 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 (ILO¹ ≥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.

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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.

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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/m³. 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

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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

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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

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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 determine 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.

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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)

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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/m³ (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 (Ni²⁺), together with other anions such as hydroxyl (OH⁻), sulfate (SO₄²⁻), chloride (Cl⁻), carbonate (CO₃²⁻), or nitrate (NO₃⁻). 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 $(\text{Ni,Fe})_9\text{S}_8$, nickeliferous pyrrhotite, $(\text{Fe,Ni})_{1-x}\text{S}$, 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 $\geq 99.8\%$ 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.

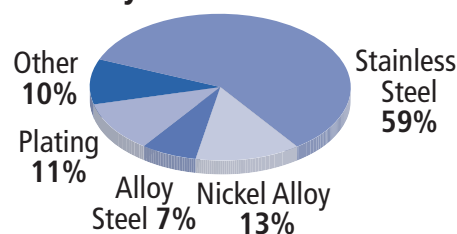
The primary nickel industry is growing and evolving. There are a number of new entrants and a number of established producers are now part of some of the largest mining companies in the world. Smelting or refining operations take place in more than a dozen countries and are fed with concentrates from 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

W. World inc China Nickel First Use 2006 by Product Form



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.

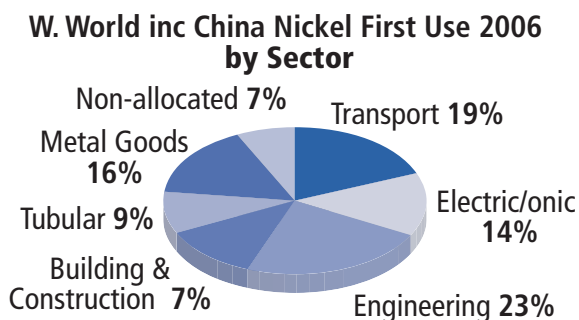
There is a constant stream of new uses for nickel where small uses of nickel are providing gains in environmental (including energy efficiency and carbon emission) performance.

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).

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.

Figure 2



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/m³), whereas average exposures in chemical blending and nickel catalyst production average 0.3-0.5 mg Ni/m³.

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

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	T ²	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 14.5×10^6 kg/year. At the same time, natural emissions from volcanism, dust storms, fires, *etc.* contribute approximately 8.5×10^6 kg/year. However, natural and industrial emissions combined are substantially less than the emissions from fuel combustion which total approximately 28.6×10^6 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 13×10^6 kg Ni/y. There are larger differences in the estimates for the contribution from other anthropogenic sources. These range from 28.6×10^6 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 8.5×10^6 kg/year (Bennett, 1984) to 1800×10^6 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 Flyvholm, 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 atmo-

sphere of the United States ranges from 0.01 to 60, 0.6 to 78, and 1 to 328 ng/m³ 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/m³ and 1 to 20 ng/m³, respectively. Nickel concentrations in indoor air are typically <10 ng/m³ (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 m³ of 20 ng Ni/m³/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 m³ of air is inhaled in an eight-hour work day (the as-

4. Pharmacokinetics Of Nickel Compounds

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/m³, 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 work-

place, 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

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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 ($^{63}\text{Ni}_3\text{S}_2$ 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 $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) 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 $330 \pm 380 \mu\text{g/g}$ in roasting and smelting workers exposed to less-soluble compounds, $34 \pm 48 \mu\text{g/g}$ in electrolysis workers exposed to soluble nickel compounds, and $0.76 \pm 0.39 \mu\text{g/g}$ 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 $50 \mu\text{g/g}$ 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 $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in rodents and monkeys and sub-chronic 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 radiolabeled 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 $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ was rapid in all species, and no impaired clearance of subsequently inhaled radiolabeled $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ was observed.

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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 ($27 \pm 17\%$) than when it was given in food ($0.7 \pm 0.4\%$) (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 $80 \mu\text{g/L}$ 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*

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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 (Rezuze *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 Ni₃S₂ and soluble NiSO₄ (as NiSO₄•6H₂O) (Dunnick *et al.*, 1989). Following intratracheal administration of Ni₃S₂ and NiSO₄, 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 NiSO₄ *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 NiSO₄ 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

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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

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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).

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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.

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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/m³), certain subgroups of workers, such as those in powder metallurgy, have been exposed to higher concentrations of metallic nickel (around 1.5 mg Ni/m³) (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, evi-

dence 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.*

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(2000) have cautioned that, in the case of intra-tracheal 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 ($\sim 1.6 \mu\text{MMAD}$) 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 decre-

ments 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 ($382 \text{ mg Ni}/\text{m}^3$) to relatively fine nickel particles.

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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 FEV₁:FVC² 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 $\geq 1/0$) (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, $\leq 100 \mu\text{m}$ particle diameter). In certain specific operations involving the manufacturing and packaging of finely divided elemental nickel powders ("respirable" size particles, $\leq 10 \mu\text{m}$ particle diameter) or ultrafine powders ($< 1 \mu\text{m}$ 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 nickel.

² Forced Expiratory Volume (FEV₁) 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%).

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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-

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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 devices 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-

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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 reac-

tions 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 µg/cm²/

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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/cm²/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/cm²/week or less (Gawkrödger, 1996). With these few exceptions, the use of 0.5 µg Ni/cm²/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 µg/cm²/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/m³), although some studies have suggested that exposures slightly lower than 1 mg Ni/m³ 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/m³). 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/m³ or 0.22 mg Ni/m³, respectively (NTP, 1996b). These concentrations correspond to approximately 2 or 6 mg Ni/m³ 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/m³, 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, *let alone* 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 $\geq 1/0$) 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 work-

places 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 NiSO₄-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 NiSO₄•6H₂O/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

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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; Vyskočil *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., β_2 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 nephrotoxics (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.* (1994) 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

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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) musculoskeletal 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 to 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; Gawkrödger *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 were 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 cap-

sule (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 co-workers (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) ox-

ides and other non-stoichiometric 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.

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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 ($>5 \text{ mg Ni/m}^3$) (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 ($<2 \text{ Ni/m}^3$) 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 com-

pounds 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-

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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/m³ 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/m³) 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 (Järup *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; Järup *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/m³). Hence, it may be that there are two variable – the physicochemical nature of the oxide and

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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/m³. These concentrations are equivalent to over 5.0 to 20 mg Ni/m³ 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/m³) and only equivocal evidence in female mice exposed to 1.0 but not 2.0 or 4.0 mg Ni/m³.

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 $\leq 5 \mu\text{m}$, 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

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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/m³), 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/m³), 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 al-

veolar 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/m³ and 1.0 mg Ni/m³, respectively (NTP, 1996c). These values correspond to workplace exposures above 5-10 mg Ni/m³. 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)₉S₈]. 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

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“sulfidic nickel” pertains mainly to nickel sulfides (NiS) and subsulfide (Ni₃S₂).

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/m³) 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/m³) 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/m³ (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/m³, respectively. These concentrations correspond to approximately 1.1-4.4 mg Ni/m³ 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-

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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/m³). 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

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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-

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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 LD₅₀ 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/m³) 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, 1999³). 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 harm⁴. 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).

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.

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.

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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 health 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 (Gawkrödger, 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 (Gawkrödger, 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

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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

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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 con-

centrations 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 urine⁵ 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 $\mu\text{mol Ni/mol creatinine}$. 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 $\mu\text{g Ni/L}$, 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 $\mu\text{g Ni/l}$ (18-hour urine specimen).
- Moderate Symptoms: 100 to 500 $\mu\text{g Ni/l}$ (18-hour urine specimen).
- Severe Symptoms: >500 $\mu\text{g Ni/l}$ (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 $\mu\text{g Ni/l}$, moderate cases as having 150-500 $\mu\text{g Ni/l}$, and severe cases as having >500 $\mu\text{g Ni/l}$ (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-

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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-

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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.

7. Workplace Surveillance

Knowledge of general exposure conditions within the workplace is another element of a worker protection program. Workplace surveillance entails understanding the applicable legislative occupational exposure limits and implementing an air monitoring program that allows for comparison of worker exposures to these limits. Both of these components are discussed in detail in this section.

7.1 Air Monitoring

Where workers are known to be exposed to nickel in the air, it is necessary to conduct air monitoring in order to determine whether worker exposures fall within permissible limits. A successful air monitoring program begins with a good understanding of the physical layout and processes of the workplace. Before any monitoring is undertaken, a visual survey of the site should be conducted in order to identify potential areas of significant exposure. Material Safety Data Sheets (MSDS) should also be reviewed and discussed with employees as another means of identifying potential problem areas. Only when these initial surveys have been completed and analyzed should the employer embark on an air monitoring program.

Characterization of exposure is a complex task that is best done by trained personnel. For facilities that lack the appropriate staff, certified occupational hygiene consultants are the suggested alternative. Governmental organizations may provide assistance on air monitoring or advice on where to obtain skilled help.

The 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 record-keeping.

Specific requirements for each of these components may differ from country to country; therefore, employers should consult the appropriate government agency or code for detailed procedures.

Air monitoring is not an end in itself but should be considered part of an overall program of risk assessment and management. Upon completion of an air monitoring survey, it is necessary to evaluate the results and decide whether any action is required to modify the sampling procedures or working environment.

Current nickel standards generally differentiate only between water-soluble and insoluble compounds and nickel carbonyl. Thus, the application of air monitoring techniques that collect total dust samples in combination with analyses that distinguish between compound solubilities has been sufficient to determine compliance. Recent work, however, indicates that health effects associated with nickel exposures may be

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dependent upon a number of factors, including chemical form (speciation), particle size, and solubility within biological fluids (as opposed to water) (see Section 5). Therefore, it is recommended that each worksite be characterized with regard to the individual nickel species present in the air and to the distribution of particle sizes in the aerosols.

New sampling instruments have been developed that measure inhalable aerosol (Mark and Vincent, 1986). The performance of these devices closely matches the human inhalation curves, adopted by the International Standards Organisation (ISO, 1984), the Comité Européen Normalisation (CEN, 1993) and the American Conference of Governmental Industrial Hygienists (ACGIH, 1993-94). The ACGIH replaced the traditional ‘total’ aerosol concept with a new sampling convention based on human inhalability in their 1998 TLV recommendations for nickel. It should be noted that side-by-side comparisons of the inhalable sampler to “total” aerosol samplers (such as the 37 mm sampler) have shown that the inhalable sampler consistently measures 2-3 times more nickel aerosol than the ‘total’ sampler. (Tsai et al., 1995; Tsai et al., 1996a and 1996b).⁶ Consequently, when epidemiological data based upon “total” measurements form the basis of a hazard identification conversions of the results will have to be performed to establish new guidelines for using “inhalable” measures (*i.e.*, the “total” values will have to be increased to account for the greater efficiency of the “inhalable” sampler).

The components of an air sampling program are briefly discussed below.

7.1.1 Sampling Strategy

The sampling strategy selected depends on the goal of the sampling program, whether it is to ascertain compliance, provide data for research, or investigate a particular workplace problem. The strategy may seek to evaluate exposures of all workers or a representative worker. Sampling may be conducted to develop an exposure profile (*e.g.* full shift sampling over several consecutive days), examine the same job on different shifts, or characterize the exposure associated with a specific task. Some strategies evaluate concentrations at the source and extrapolate these results in order to estimate worker exposure. Alternatively, sampling might be conducted to determine the source of exposure where potential “problem areas” have been identified through biological monitoring but where the source of exposure has not been identified.

The development of a sampling protocol which allows hygienists to evaluate exposure to Ni-containing aerosols relative to occupational exposure limits has recently been completed (Rappaport *et al.*, 1995; Lyles and Kupper, 1996). This protocol explicitly recognizes both within- and between-worker sources of exposure variability. Thus, overexposure is defined as the probability that a randomly selected worker would have a mean exposure above the exposure

⁶ More information on this research is available from NiPERA.

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limit, for a particular time period. In addition, this protocol provides guidelines that would allow for the collection of solid and reliable data for future epidemiological studies.

Since operating conditions and individual methods of work can vary enormously, exposure monitoring of the workplace tends to be an inexact science. It is therefore important that the sampling strategy be flexibly designed to account for differences in worker and job variability and to obtain statistically valid results. This may mean that different sampling strategies should be employed in different areas of a plant. Other sources of information on sampling strategies include the aforementioned HSE in the U.K. and OSHA in the U.S., as well as the U.S. National Institute for Occupational Safety and Health (NIOSH).

7.1.2 Monitoring Frequency

Considerations in determining monitoring frequency should include: regulatory requirements, changes in the process, work practices or other factors that affect exposure, and evidence of health effects. Periodic monitoring can be used to evaluate the effectiveness of exposure controls and control equipment maintenance programs.

7.1.3 Equipment

Simply described, an air sampling device consists of an electrically-operated air sampling pump, sampling medium, and tubing to connect the medium to the pump. This equipment may be portable and worn on a worker, generally for an eight-hour (one-shift) period, or it may be static with long-lasting batteries or connection to a main supply of electricity. The sampling media may be a filter, solvent, or solid absorbent. Possible contact sources for names and addresses of manufacturers and suppliers of environmental monitoring equipment are listed in Appendix A. Filter media and filter holders may be purchased through suppliers and assembled in-house or can be bought pre-assembled. Personal and/or static sampling devices may be used depending upon the requirements of the sampling program, but it is important to note that static sampling frequently underestimates exposures.

A second type of device available for estimating the concentration of soluble aerosols of nickel is the detector tube with manual pump. Soluble airborne contaminants produce a color change as the pump draws the air through the detector tube. The length of the stain is proportional to the concentration. Since the typical accuracy of these readings is ± 25 percent and the lower limit of detection is 0.25 mg Ni/m^3 , this device should serve only as a screening tool to aid in deciding whether to conduct full shift monitoring. It should also be noted that FeSO_4 interferes by producing a similar color change. A detector tube is also available for nickel carbonyl. However, as its detection limit is only 0.1 ppm , its use is limited.

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Selecting the appropriate equipment depends on the goal behind sampling and any specifications established by the regulating authority. Pumps are generally interchangeable since they all have similar functions, but dust collection methods vary depending on whether particle-size-selective sampling of the dust is desired. Furthermore, some filtering media can be used to distinguish between different forms of nickel more readily than others. Therefore, the objectives of the sampling program and guidelines or regulations that apply should be determined before selecting the sampling equipment (see Section 7.2).

Manufacturers, suppliers, industry trade associations, or associations that support occupational health professionals may be sources of sampling information. Appendix A lists some possible contacts for these sources. Another alternative is to use published methods such as those prepared by NIOSH (1994a, b, c).

In addition to the air sampling device, calibration and quality control are fundamental to valid monitoring results. Equipment to calibrate the volumetric flowrate of the air sampling device is essential. Soap bubble meters, rotameters, or automated instruments may be used for such purposes and are available through equipment manufacturers and suppliers.

7.1.4 Sampling Technique

For personal sampling, the position of the sampling medium should allow the device to collect air from the employee's breathing zone. This is defined by OSHA in the U.S. as a two-foot diameter sphere centered in the middle of the head. For welders, the filter medium should be placed inside the welding helmet because the helmet provides some protection and inaccurate results would be obtained otherwise. The pump, which is frequently worn on a belt, and the tubing should not impede the worker's activities or pose a safety hazard.

In all cases, the employees' support should be sought by explaining the reason for sampling and asking for their participation. Employees should also be instructed to notify the supervisor or person conducting the sampling if the equipment malfunctions or if they need to have it removed.

During the shift, periodic checking of the battery charge and pump flowrate should be performed and documented to ensure sample validity and accurate volume calculation. This is especially important in very dusty operations where high filter loadings may occur and cause the pump flowrate to decrease. Some pumps are designed to compensate for this by automatically increasing the pump speed and, thus, the flowrate; however, periodic checks are still recommended. The person doing the sampling should also note the temperature and barometric pressure so that adjustments to the volume of air collected can be made.

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Through work observation, a job description should be developed that includes information about work practices and other factors that potentially influence exposures. This can be used to explain sample results and to aid in decisions on exposure control should the need arise. This information may include production rates, time spent on breaks, the use of ventilation, work practices, and proximity to the source of exposure. In addition to recording descriptive information and documenting pump checks, the collection sheet can serve as a log for ambient conditions relevant to sample collection, pump and filter media identification numbers (including sample blanks), and sample duration. Any use of respiratory protection also should be documented.

7.1.5 Sample Analysis

Several methods exist for analyzing samples. The most common method is to treat the sampling filter with an appropriate acid solution, thereby releasing the entrained nickel for subsequent analysis by atomic absorption. The definitive method has been described by the International Union of Pure and Applied Chemistry (IUPAC) (Brown *et al.*, 1981). X-ray spectrometry of the filter is a simple and accurate alternative if the equipment is available. In samples with relatively high concentrations of nickel ($\mu\text{g/g}$ or $\mu\text{g/dl}$ range) Inductively Coupled Plasma - Atomic Emission Spectrometry (ICP-AES) allows multi-element detection including the reliable analysis of nickel ions.

Speciation currently is used only as a research procedure since it is time consuming and expensive. As the importance of speciation has already become more widely recognized by researchers and regulators alike, it may become more commonplace, or even mandatory, to analyze samples for specific species. Alternatively, it may be considered adequate first to characterize the workplace atmosphere by a detailed species analysis (Zatka *et al.*, 1992) and then use conventional methods to measure total nickel and apportion the results to specific species.

In selecting a method, an important consideration is the requirements of the applicable regulations. These regulations may require that the laboratory conducting the analysis participate in a qualification or certification program to ensure accurate results. If no regulations exist, then the objectives in sampling should help determine the choice of analytical methods. Evidence of effective quality control will be essential. Contacts and resources for additional guidance are listed in Appendix A. Whenever possible, the selected sampling procedure should be discussed with the laboratory that will perform the analysis prior to sampling. Frequently, the laboratory can also provide valuable guidance on potential interferences, the number of samples and field blanks needed, sample storage, and transportation.

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7.1.6 Calculating Exposure Results

An employee's time-weighted average exposure concentration ("TWAEC") is calculated by taking the sum of the products of the analytically-determined concentration for each sampling period, including overtime (see Appendix B), and the duration of the corresponding sampling period and dividing this sum by the total sampling time as shown in the equation below:

$$\frac{C_1 T_1 + C_2 T_2 + \dots + C_n T_n}{T_1 + T_2 + \dots + T_n}$$

where:

C_n = concentration for sample n in mg/m^3 ,
and

T_n = sampling time for sample n in minutes.

Because sampling time rarely equals eight hours exactly, a decision regarding exposures during any unsampled periods must be made before comparing the result to eight-hour TWA standards (see Appendix B).

7.1.7 Determining Compliance

Since procedures for determining compliance may vary from country to country, the employer should understand the appropriate regulatory requirements for the specific locale where operations are being carried out. A number of statistical techniques are published that allow determination of compliance with an associated degree of confidence. In most cases, data collected from portable personal sampling equipment will be preferred over those collected from static samplers.

7.1.8 Employee Notification

Good industrial hygiene practices encourage the employer to provide the sampled individuals who have co-operated in the air monitoring program (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 a "representative" individual or representative individuals made available to other workers, consideration should be given to withholding personal identifiers. Some authorities may require this notification and specify a date by which this should be done relative to the date of receipt of the results.

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7.1.9 Record-keeping

Some countries may require that exposure records be maintained by the employer for a number of years. For example, in the U.S., this record-keeping is required for at least 30 years from the date on which the exposure measurement is taken. In the EU, the requirement is for at least 40 years following exposure. Regulations generally require that employees (and possibly their representatives as well) be granted access to these records. Any exposure monitoring data gathered and recorded should be subject to rigorous quality control. The International Organization for Standards (ISO) has developed a set of useful guidelines for implementing a quality assurance program (see Appendix A for a possible contact).

7.2 Carcinogenic Classifications

In recent years, a number of organizations and international agencies have evaluated the evidence regarding the carcinogenic effects of nickel, all with the intent of delineating the potential differences in the bioavailability and toxicity of various nickel species.

Based largely on the 1990 findings of the ICNCM, the IARC concluded that there is sufficient evidence in humans for the carcinogenicity of nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel refining industry. Conversely, it concluded that there is inadequate evidence in humans for the carcinogenicity of metallic nickel and nickel alloys. Based upon its evaluation of both human

and experimental data, the IARC has classified nickel compounds as Group 1 (carcinogenic to humans) and metallic nickel as Group 2B (possibly carcinogenic to humans) (IARC, 1990).

In a 1986 evaluation, the U.S. Environmental Protection Agency (U.S. EPA) classified nickel subsulfide and nickel refinery dust from pyrometallurgical sulfide nickel matte refineries as Group A carcinogens, indicating that there is sufficient overall evidence that these forms of nickel are carcinogenic to humans (U.S. EPA, 1986). The Agency also classified nickel carbonyl as a Group B2 probable carcinogen. However, this classification was based upon a rodent study showing somewhat questionable statistical results.

The American Conference of Governmental Industrial Hygienists (ACGIH) (a non-legislative organization) published a list of proposed changes to carcinogen classifications and TLVs for nickel compounds in January, 1997. The ACGIH carcinogen classifications for nickel compounds are:

- A5 (not suspected as a human carcinogen) for metallic nickel,
- A4 not classifiable as a human carcinogen) for soluble nickel,
- A1 (confirmed human carcinogen) for insoluble nickel,
- A1 for nickel subsulfide, and
- no classification for nickel carbonyl.

In 2008, the Commission of the European Communities will conclude an extensive

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evaluation of the human health and environmental effects of metallic nickel and a group of nickel compounds including nickel sulfate, nickel chloride, nickel nitrate, nickel carbonate, nickel sulfides (Ni_3S_2 and NiS) and nickel oxides (NiO , Ni_2O_3 and NiO_2). As a result of this hazard and risk assessment, all these nickel compounds (except metallic nickel) will be classified as human carcinogens (Table 7-1). Category 1 carcinogens are “*Substances known to be carcinogenic to man*”. The above nickel compounds have been assigned the risk phrase, “May cause cancer by inhalation” which specifically eliminates the potential for carcinogenicity by other routes of exposure (*e.g.*, oral). Nickel metal will be classified as a Category 3 carcinogen, “*Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.*”

For more information on the carcinogenicity of nickel, its compounds and alloys, the reader is referred to the Agency for Toxic Substances and Disease Registry August 2005 profile on nickel and nickel compounds (ATSDR, 2005) and the original ICNCM Report (ICNCM, 1990).

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Endpoint	Nickel Sulfate		Nickel Chloride		Nickel Nitrate		Nickel Carbonate Hydroxide		Nickel Hydroxide		Nickel Sulphide		Nickel Monoxide		Metallic Nickel#	
	EU	Expected GHS	EU	Anticipated GHS	EU	Anticipated GHS	EU	Anticipated GHS	EU	Anticipated GHS	EU	Anticipated GHS	EU	Anticipated GHS	EU	Anticipated GHS
Endpoint	CAS: 7786-81-4		CAS: 7718-54-9		CAS: 13138-45-9; 14216-75-2		CAS: 3333-67-3; 16337-84-1; 65405-96-1; 12607-70-4		CAS: 1205448-7		CAS: 16812-54-7; 11113-75-0		CAS: 1313-99-1; 11099-02-8; 34492-97-2		CAS: 7440-02-0	
											Sub-sulphide		Dioxide			
											CAS: 12035-72-2; 12035-71-1		CAS: 12035-36-8			
													CAS: 1314-06-3			
	EINECS: 232-104-9		EINECS: 231-743-0		EINECS: 236-068-5; 238-076-4		EINECS: 240-408-8; 222068-2; 265-748-4; 235-715-159		EINECS: 235-008-5		EINECS: 240-841-2; 234-349-7; 234-829-6		EINECS: 215-215-7; 234-323-5; 234-823-3; 215-217-8		EINECS: 231-111-4	
Physical Properties	None	None	None	None	O;R8	None	None	None	None	None	None	None	None	None	None	None
Acute Oral	Xn;R22	Cat3	T;R25	Cat3	Xn;R22	Cat3 BBL=Cat4	Xn;R22	Cat3	Xn;R22	Cat3	None	None	None	None	None	None
Acute Inhalation	Xn;R20	Cat3	T;R23	Cat3	Xn;R20	Cat3 BBL=Cat4	Xn;R20	Cat3	Xn;R20	Cat3	None	None	None	None	None	None
Dermal Irritation	Xi;R38	Cat3	Xi;R38	Cat3	Xi;R38	Cat2	XiR38	Cat3	Xi;R38	Cat3	None	None	None	None	None	None
Eye Irritation	None	None	None	None	Xi;R41	Cat1	None	None	None	None	None	None	None	None	None	None
Dermal Sensitization	R43*	Cat1	R43*	Cat1	R43*	Cat1	R43	Cat1	R43	Cat1	R43	Cat1	R43	Cat1	R43**	Cat1
Respiratory Sensitization	R42	Cat1	R42	Cat1	R42	Cat1	R42	Cat1	R42	Cat1	None	None	None	None	None	None
Chronic Toxicity	T;R48/23	Cat1 BBL=Cat2	T;R48/23	Cat1 BBL=Cat2	T; R48/23	Cat1 BBL=Cat2	T;R48/23	Cat1	T;R48/23	Cat1	T;R48/23	Cat1	T;R48/23	Cat1	T;R48/23	Cat1 BBL=Cat2
Reproductive Toxicity	Cat2;R61	Cat1B BBL=Cat2	Cat2;R61	Cat1B BBL=Cat2	Cat2;R61	Cat1B BBL=Cat2	Cat2;R61	Cat1B(2)*	Cat2;R61	Cat1B(2)*	None	None	None	None	None	None
Mutagenicity	Cat3;R68	Cat2 BBL=None	Cat3;R68	Cat2 BBL=None	Cat3;R68	Cat2 BBL=None	Cat3;R68	Cat2 (None)*	Cat3;R68	Cat2 (None)*	Cat3;R68	Cat2	None	None	None	None
Carcinogenicity	Cat1;R49	Cat1A	Cat1;R49	Cat1A	Cat1; R49	Cat1A	Cat1; R49	Cat1A	Cat1; R49	Cat1A	Cat1; R49	Cat1A	Cat1; R49	Cat1A	Cat3; R40	Cat2 (None)*
S-Phrases	53, 45, 60, 61		53, 45, 60, 61		53, 45, 60, 61		53, 45, 60, 61		53, 45, 60, 61		53, 45, 60, 61		53,45,61		36,37,45	
Aquatic Environment	[N;R50/53]	Acute1 Chronic1	[N;R50/53]	Acute1 Chronic1	[N;R50/53]	Acute1 Chronic1	[N;R50/53]	Acute1 Chronic1	[N;R50/53]	Acute1 Chronic1	[N;R50/53]	Acute1 Chronic1	[N;R53]	Chronic1	Powder (<1mm diameter): R52/53 Massive: None	Powder (<1mm diameter): Acute3 Chronic3 Massive: None
Blue type denotes a change from previous classification						Blue background denotes equivalent GHS classifications										

NOTE: This table shows the results of a direct conversion of the 30th ATP EU classifications for the listed nickel compounds to the GHS system (in blue). The reference to "BBL" classifications is derived from a project completed by a consulting firm hired by the NI to review the toxicology data in the EU RA and use their own scientific judgment to translate the EU classifications into GHS. BBL proposed GHS classifications for nickel sulphate, chloride, nitrate and metal. BBL did not look at nickel carbonate, hydroxide, oxide or sulfide.

- ^ = By analogy to the BBL interpretation of classification for water soluble nickel compounds since derogation from water soluble compounds was used by the EU for nickel carbonate classification. The nickel hydroxide classification was read-across from nickel carbonate.
- ^^ = This classification may change based upon a recent negative animal carcinogenicity study and the lack of epidemiological data.
- * 0.01% concentration limit
- ** concentration limit based on release rate of 0.5 µg Ni/cm²/week

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Nickel Sulphate: C>25%: T, N ; R49-61-20/22-38-42/43-48/23-68-50/53; 20%<C≤25%: T, N; R49-61-38-42/43-48/23-68-51/53; 2.5%<C≤20%: T, N; R49-61-42/43-48/23-68-51/53; 1%<C≤2.5%: T; R49-61-42/43-48/23-68-52/53; 0,5%<C≤1%: T; R49-61-43-48/20-52/53; 0,25%<C

Nickel Chloride: C>25%: T, N ; R49-61-23/25-38-42/43-48/23-68-50/53; 20%<C≤25%: T, N; R49-61-20/22-38-42/43-48/23-68-51/53; 3%<C≤20%: T, N; R49-61-20/22-42/43-48/23-68-51/53; 2.5%<C≤3%: T, N; R49-61-42/43-48/23-68-51/53; 1%<C≤2.5%: T; R49-61-42/43-48/23-6

Nickel Nitrate: C>25%: T, N ; R49-61-20/22-38-41-42/43-48/23-68-50/53; 20%<C≤25%: T, N; R49-61-38-41-42/43-48/23-68-51/53; 10%<C≤20%: T, N; R49-61-41-42/43-48/23-68-51/53; 5%<C≤10%: T, N; R49-61-36-42/43-48/23-68-51/53; 2.5%<C≤5%: T, N; R49-61-42/43-48/23

R8 = Contact with combustible material may cause fire

R11 = Highly flammable

R20 = Harmful by inhalation

R22 = Harmful if swallowed

R23 = Toxic by inhalation

R25 = Toxic if swallowed

R36 = Irritating to eyes

R38 = Irritating to skin

R40 = Limited evidence of a carcinogenic effect

R41 = Risk of serious damage to eyes

R42 = May cause sensitization by inhalation

R43 = May cause sensitization by skin contact

R45 = May cause cancer

R49 = May cause cancer by inhalation

R50 = Very toxic to aquatic organisms

R53 = May cause long term adverse effects in the aquatic environment

R61 = May cause harm to the unborn child

R63 = Possible risk of harm to the unborn child

R68 = Possible risk of irreversible effects

R48/23 = Toxic-danger of serious damage to health by prolonged exposure through inhalation

0 = Oxidizing

Xi = Irritating

Xn = Harmful

T = Toxic

N = Dangerous for the environment [Note: Currently applies to sulphate, chloride, nitrate, and carbonate (not metal), but subject to modification by the Environment TC C & L.

S2 = Keep out of the reach of children

S36/37 = Wear suitable protective clothing and gloves.

S45 = In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

S53 = Avoid exposure – obtain special instructions before use.

S60 = This material and its container must be disposed of as hazardous waste.

S61 = Avoid release to the environment. Refer to special instructions/safety data sheets.

Note E: Substances with specific effects on human health (see chapter 4 of Annex V1 of Directive 67/1548/EEC) that are classified as carcinogenic, mutagenic, and/or toxic for reproduction in categories 1 or 2 are ascribed Note E if they are also classified as very toxic (T+), toxic (T) or harmful (Xn). For these substances, the risk phrases R20, R21, R22, R23, R24, R25, R26, R27, R28, R39, R68 (harmful), R48 and R65 and all combinations of these risk phrases shall be preceded by the word 'Also'."

Note U is a new note agreed to be included in the foreword to Annex I reading as follows: Alloys containing nickel are classified for skin sensitisation when the release rate of 0.5 µg Ni/cm2/week as specified in the European Parliament and Council Directive 94/27/EC and as measured by the European Standard reference test method, EN 1811 is exceeded.

8. Control Measures

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

- engineering controls,
- administrative controls,
- work practice controls, 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. Feasibility issues fall into two categories: technological feasibility and economic feasibility. Technological feasibility can generally be determined by examining the use of the technology in similar industries or for similar processes. Independent studies available from regulatory agencies, trade associations and other industry support groups or reported in journals or other publications can also shed light on the issue. Determination of economic feasibility may require that a facility- or company-specific impact evaluation be made. Employers should be aware that regulatory authorities may already have determined that feasible engineering controls to achieve the OEL are available for particular industries or types of operation.

8.1 Engineering Controls

Three categories of engineering controls are generally considered: substitution, enclosure, and exhaust ventilation. Substitution may involve replacing the actual contaminant or replacing the source of the contaminant with one that produces lower concentrations. One consideration in

substitution is to avoid introducing a new hazard when replacing the original hazard. Enclosure can mean either enclosing the source or the exposed individual. The source may also be remotely located so that little or no exposure results. Of the three engineering controls, however, ventilation is the most relevant to this document and is discussed in greater detail below.

8.1.1 Exhaust Ventilation

Local exhaust ventilation provides contaminant capture or dispersion at or near the source. This form of ventilation can range from the very simple, such as the use of fans, to the more complex, such as the use of an exhaust hood positioned at the source. In all instances, the goal is to blow or draw the contaminant away from the breathing zones of the workers. Examples of local exhaust ventilation include:

- exhaust fans positioned over furnaces,
- exhaust hoods for points of transfer on dusty operations,
- slot hoods for electroplating tanks,
- ventilated metal spraying booths,
- downdraft tables for finishing (grinding) of cast iron pieces, and
- portable exhaust hoods for welding operations.

Ventilation design is a complex and expensive process that needs to be undertaken by suitably trained engineers who are familiar not only with industrial ventilation design but also with methods used to control exposures and protect worker health. The designer should consider: (1) the regulations that govern the release of the workplace contaminant to the surrounding environment, and (2) the process operation, including

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any materials used and the frequency with which they are handled. Particular attention should be paid to packaging processes involving fine materials. With respect to process operations, it is less expensive and more effective to use specialized and dedicated equipment introduced at the design stage than to retro-fit such equipment to an existing facility.

8.1.2 Dilution Ventilation

Dilution ventilation relies on adequate circulation of fresh air in the room to dilute the contaminant concentration. This type of ventilation has a number of limitations:

- workers close to the air contaminant's source may be exposed to high, localized concentrations of the contaminant,
- dilution ventilation systems are affected by weather conditions (doors or windows are kept open or closed depending on the temperature) and the movement of objects and people in a room, and
- if the rate of contaminant generation increases, the dilution supplied may be inadequate.

Given these limitations, such systems are usually not recommended for contaminants that are highly or moderately toxic.

8.2 Administrative Controls

Administrative controls reduce the exposure duration of individuals, thereby reducing the employee's overall exposure. Two alternatives are employee rotation and work shift modification. There are, however, drawbacks to these controls including:

- it may not be feasible to rotate employees with sufficient frequency to comply with the exposure limit (more frequently than every two hours is generally considered to be infeasible),
- the workers may not be versatile enough to perform different jobs, and
- greater management involvement is required.

Modifications in shift patterns are never easy. Effective exposure reduction by these techniques also requires that a constant contaminant level be present. For intermittent processes or where production rates vary between shifts, the differing levels of activity cause fluctuations in contaminant concentrations that may make average exposures difficult to quantify or predict. Because of these limitations, administrative controls should be considered secondary to engineering controls and other work practices that may be more effective in controlling exposures.

8.3 Work Practice Controls

Work practice controls are procedures that serve to limit employee exposures. The effectiveness in reducing exposures thus relies heavily on worker training and the use of standard operating procedures. Some examples of good work practices are the routine use of available local exhaust ventilation, the use of wetting agents to reduce dust levels and the observance of good housekeeping and personal hygiene practices. Housekeeping practices should include routine cleanup of the work area, particularly for dusty processes. However, the clean up activities themselves should not raise dust that may increase exposures. For example, dry sweeping may need to be prohibited and replaced by vacuum cleaning systems fitted with appropriate filters.

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Good personal hygiene is important in all jobs and should be encouraged. Employees should be encouraged to change contaminated clothing in order to reduce the risk of contact dermatitis and of inhalation of nickel-bearing dust from contaminated clothing. If necessary, changes of work clothing and shower facilities should be made available. In areas where moisture, exposure to solvents, or wet working increases skin irritation (and thus, the possibility of developing nickel sensitization) appropriate protective clothing should be provided.

Particular attention should be given to the selection and maintenance of gloves. Some latex gloves can cause their own form of allergic contact dermatitis called latex glove contact urticaria (LGCU). LGCU can be avoided by wearing gloves made from polyvinyl chloride or synthetic rubber or by wearing cotton or plastic undergloves (Turjanmaa and Reunala, 1991). Once gloves or gauntlets impervious to soluble salts, their solutions and/or powders have been selected, they should be washed and tested for leaks daily and replaced whenever found to be faulty.

Because smoking is the most common cause of respiratory cancer, it should be discouraged, if not banned. Appropriate educational materials and smoking cessation programs can play an important role in reducing cigarette smoking. In the interest of good hygiene, the consumption of beverages or food in nickel exposure areas should be discouraged, with attempts to confine such activity to designated eating areas. Some regulatory bodies have already mandated such practices. Hence, in EU countries, smoking, eating, and drinking are prohibited in areas where there is a risk of contamination by carcinogens.

8.4 Personal Protective Equipment (PPE)

PPE ordinarily is the last control option considered. Situations where use of PPE may be recommended include:

- while engineering controls are being installed,
- when current engineering controls are insufficient to reduce exposure to acceptable levels and administrative controls are not practical (the installation of additional feasible controls should be considered),
- when engineering and administrative controls are not feasible or practical or an emergency exists, and
- when intermittent, short-term exposures may not merit major engineering, *e.g.*, in maintenance.

With respect to the latter situation, special attention should be paid to the use of PPE by maintenance personnel. Maintenance conditions typically differ from routine operations. For example, contaminant concentrations are frequently higher because of the very nature of the maintenance problem or because the ventilation system has been deactivated in order to allow the worker to perform the maintenance activity. Instituting certain work practice controls may be helpful in such circumstances, but additional personal protective equipment is frequently needed.

Emergency use of PPE requires additional planning and training. Special procedures for each potential emergency should be developed and practiced regularly.

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Regardless of the situation in which PPE is used, the effectiveness of PPE in controlling exposures ultimately depends upon the correct selection and use of the equipment. As recommendations on this use may vary from country to country, employers should contact their appropriate regulatory authority for guidance. Use of PPE should always occur under a properly administered program.

8.4.1 Respirators

The main types of protective equipment in use for nickel exposures are those designed to provide respiratory protection.⁷ Of particular importance is the use of respirators. Respirators may be used as an exposure control measure under certain circumstances. An appropriate authority should be consulted for guidance on respirator use (see below). Respirator use in fire fighting and similar emergencies is beyond the scope of this document.

The first step in developing a program for the effective use of respirators is to establish a written policy, including the following:

- management and employee responsibilities,
- respirator selection,
- respirator fitting, including in some circumstances, fit-testing,
- employee instruction and training, including procedures for cleaning, inspection, maintenance and storage,
- medical screening and
- program evaluation.

⁷ Although not specific to the nickel industry, the need for equipment to protect eyes, face, ears, head, and feet also may need to be considered, depending upon the task to be performed.

Some jurisdictions have detailed rules for respirator use. The European Directive 88/656/EEC on the use of PPE governs the use of respirators in the EU. In the U.S., OSHA enforces Standard 1910.134 [29 Code of Federal Regulations (CFR) 1910.134] for respiratory protection of workers. In Canada, provincial government agencies have regional-specific requirements.

8.4.1.1 Respirator Selection

The criteria for selection should be clearly stated in the respiratory protection program. For nickel and nickel compounds, these should include such factors as the possible concentration of the contaminants present, the particle size(s) encountered, the toxicity of the chemicals, and the limitations of the respirators. The concentration of the contaminant will dictate whether a half-face, air purifying respirator is appropriate, or whether a higher level of protection, such as that provided by a supplied air respirator, is required. Once the employer has established that the hazardous conditions do not include oxygen deficiency, toxic gases, or atmospheres otherwise immediately dangerous to life and health, a determination of the protection needed should be calculated. The minimum protection factor needed is the ratio of the exposure concentration to the exposure limit. Any respirator tested should have a rated protection factor at least as large as this ratio (Table 8-1). Quantitative fit testing is required to ensure that the respirator performs as desired.

Nickel and its compounds will generally be in particulate form such as dusts (solid particulate), mists (liquid condensation particulate), and fume (solid condensation particulate, usually as oxidized forms of nickel). Filters appropriate to each

8. Control Measures

form are available as single-use respirators or in canisters and cartridges that attach directly to molded facepieces. In the case of powered, air-purifying respirators, the canisters are attached to the facepiece with a hose. The fit of a respirator with a molded facepiece is more readily determined than is the fit of a single-use respirator, but the latter is generally more comfortable.

High concentrations of the nickel compound may require the use of supplied air by either an airline or battery powered respirator or a self-contained breathing apparatus (SCBA). Airline respirators and battery powered respirators provide a continuous supply of air for long durations. The SCBAs, on the other hand, have a limited air supply (from 30 minutes to 4 hours) but allow for a greater degree of mobility and, because of the positive pressure, have a higher protection factor. Use of a SCBA requires significant training and a health assessment of the worker.

When selecting air purifying respirators, employers should consider assigning each employee his/her own respirator. Care and maintenance, thus, become a matter of personal importance, and the responsibility for the health of a worker is shared between employer and employee. Each employee should ensure that the respirator issued fits properly and hence provides the intended degree of protection. In some jurisdictions, respirator fit-testing is mandatory.

Table 8-1: Protection Factors for Respirators Used for Particulates

Protection Factor	Respirator Type
5	Single use
10	<ul style="list-style-type: none">▪ Half- and full-face, air-purifying, any type of particulate filter▪ Half-face, supplied air, demand mode
25	<ul style="list-style-type: none">▪ Powered air-purifying, hood or helmet, any type of particulate filter▪ Supplied air, hood or helmet, continuous flow mode
50	<ul style="list-style-type: none">▪ Full-face, air purifying, HEPA filters▪ Powered air-purifying, tight facepiece, HEPA filters▪ Supplied air, full-face, demand mode▪ Supplied air, tight-facepiece, continuous flow mode▪ SCBA, full-face, demand mode
1,000	<ul style="list-style-type: none">▪ Supplied air, half-face, pressure demand or positive pressure mode
2,000	<ul style="list-style-type: none">▪ Supplied air, full-face, pressure demand or positive pressure mode
10,000	<ul style="list-style-type: none">▪ Supplied air, full-face, pressure demand or positive pressure mode with an auxiliary SCBA, pressure demand or positive pressure mode▪ SCBA, full-face, pressure demand or positive pressure mode
<i>Source: National Institute for Occupational Safety and Health (1987).</i>	

9. Limit Values And Hazard Communication

A number of countries and jurisdictions have established specific regulatory requirements for hazard communication relating to the handling, use 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.

In 1990, the International Labour Organization (ILO) published a report, *Safety in the Use of Chemicals at Work*, as a reference source for both producers and users of chemicals, including metals and metal alloys. Generally speaking, three components were identified by the ILO as composing 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 customers. Worker training is the responsibility of all employers, regardless of industry sector. As important differences may exist between jurisdictions, some of the general requirements of selected countries or regions currently implementing such programs are briefly noted in this section. Employers should contact their relevant authorities for further detailed information on such programs and any specific requirements pertaining to nickel.

9.1 Exposure Limits

If proper precautions are taken, occupational exposures to nickel, its compounds, and alloys can be adequately controlled.

Information on current workplace exposures suggests that, in general, they are significantly below the levels that were predominantly observed to be associated with excess respiratory cancers in the past – namely $>10 \text{ mg Ni/m}^3$ for less soluble nickel compounds (notably, sulfidic and oxidic nickel) and $>1 \text{ mg Ni/m}^3$ for soluble compounds (ICNCM, 1990).

Although the mechanism of nickel carcinogenicity is still unknown and the precise health risks, if any, of exposures to low levels of nickel are uncertain, governmental authorities have adopted recommended or mandated maximum exposure levels designed to protect the worker adequately.

These Occupational Exposure Limits (OELs) apply to a typical worker whose shift operates eight hours per day, five days per week. In addition to the eight-hour, time-weighted average (TWA), several countries have limits or guidelines for short-term exposures as well. Some countries allow exposures up to a specified concentration for a short time period; others specify “ceiling” concentrations that should never be exceeded. A number of standards apply to specialized operations. Some OELs are strictly health-based; others may take both health and feasibility into consideration. Occupational exposure limits for selected countries are provided in Table 9-1. Employers operating in jurisdictions which have not adopted an OEL for nickel may wish to consider the OELs that have been adopted elsewhere.

9.1.1 Australia

The National Occupational Health and Safety Commission (NOHSC) is responsible for recommending workplace exposure standards, as well as attending to other health and environmental

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matters, including those that may pertain to nickel. Historically, the NOHSC exposure recommendations have corresponded to the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLVs) (see Section 7.1.5). As such, the current workplace exposure recommendations of the NOHSC are 1.0 mg Ni/m³ for metallic and water-insoluble forms of inorganic nickel and 0.1 mg Ni/m³ for water-soluble nickel forms. The recommendation for nickel carbonyl is 0.12 mg Ni/m³.

While the NOHSC can recommend exposure limits, it is the individual State Governments which have responsibility for actually setting and implementing standards. The State Governments usually impose standards which are in keeping with the NOHSC recommendations, but they may impose more stringent standards if deemed necessary.

9.1.2 Canada

The Canadian regulatory system for occupational safety and health is divided between two separate jurisdictions: federal and provincial. Labour Canada only has jurisdiction over federal agencies and their employees; the provinces are responsible for all other workers through their respective ministries of labor and separate occupational safety and health acts. Under the Canada Labour Code, Part II, Chapter L2, the nickel exposure limits for federal employees, expressed as time-weighted average exposure values ("TWAEVs"), are 1.0 mg Ni/m³ for nickel metal, oxides and sulfides and 0.1 mg Ni/m³ for water-soluble nickel compounds. The TWAEV for nickel carbonyl is 0.12 mg Ni/m³.

The OELs for non-federal employees can vary from province to province. For example, Ontario's Occupational Health and Safety Act states: "An employer shall...take every precaution reasonable in the circumstances for the protection of a worker...." The Ontario Ministry of Labour is authorized to inspect workplaces, issue orders to employers mandating compliance, and develop regulations under the Occupational Health and Safety Act. Specifically, exposure limits have been mandated under the Regulation Respecting Control of Exposure to Biological or Chemical Agents (654/86). Expressed as TWAEVs, the limits for nickel are the same as the aforementioned limits for federal employees (Table 9-1).

These limits, like those in a number of other countries, are based on the work of the ACGIH. However, Ontario is currently reviewing, through a bipartite process involving the participation of labor and management, all regulations applicable to hazardous substances in the workplace including OELs. To date, no changes in the OELs for various forms of nickel in Ontario have been indicated.

9.1.3 The European Union (EU)

Within the EU, legislation is currently being developed with respect to workplace monitoring. Two directives exist (81/1107/EEC and 88/642/EEC) that are relevant to monitoring in general, and a third is in preparation. To date, there is no occupational exposure limit for nickel legislated within the EU, but the subject is currently under review.

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A “directive” is an official rule adopted by the Council or the Commission under the authority of the Treaties of Rome, Paris or, most recently, Maastricht. A directive is made to member countries mandating them to introduce the rule into their own legislation within a certain period of time. Some directives have to be introduced unchanged, *e.g.*, those that are designed to prevent unfair barriers to trade. Others may be changed to allow a member country to introduce a stricter law, if it so wishes, but a country cannot mandate legislation that is less stringent than the position taken in the directive. Exposure limit and worker protection legislation comes under this latter category. Until the EU has issued a directive on any particular subject, the national rules apply.

9.1.3.1 United Kingdom (U.K.)

The U.K. is a member state of the EU. It administers its occupational exposure laws through the Health and Safety Commission (HSC) and the Health and Safety Executive (HSE), both of which were established under the Health and Safety at Work Act of 1974. The HSC is a tripartite group representing industry, government, and labor. It sets policy and oversees the HSE which is the governmental enforcement agency. The 1988 Control of Substances Hazardous to Health or “COSHH” Regulations, which implement the Health and Safety at Work Act, states: *“Every employer shall ensure that the exposure of his employees to substances hazardous to health is either prevented or, where this is not reasonably practicable, adequately controlled.”* The COSHH regulations came into force on October 1, 1990. Under these regulations there are two classes of occupational exposure:

- MEL – Maximum Exposure Level
This is the maximum concentration of an airborne substance averaged over a reference period (generally eight hours) to which employees may be exposed by inhalation under any circumstances.
- OES – Occupational Exposure Standard
This is the concentration of an airborne substance averaged over a reference period at which, according to current knowledge, there is no evidence that there are likely to be injuries to employees if they are exposed by inhalation day after day to said concentration.

These definitions and the actual values are published in an HSE guidance note, EH40, which is issued annually. In practice, nickel metal and water-insoluble nickel compounds currently have MELs of 0.5 mg Ni/m³ while the MEL for water-soluble nickel is 0.1 mg Ni/m³. There is a ten-minute short-term OES for nickel carbonyl of 0.24 mg Ni/m³. In addition, the European Carcinogens Directive has been translated in the U.K. into an “advisory code of practice” under COSHH, effective January 1, 1993.

9.1.3.2 Germany

Rules for limiting exposure to hazardous substances in the workplace are published in Germany by the Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin - BAuA) in Technical Rules for Hazardous Substances (Technische Regeln für Gefahrstoffe) TRGS 900: Occupational exposure limits (Arbeitsplatzgrenzwerte). This document was re-issued in January 2006 with significant changes to the list of substances for which occupational exposure limits have been assigned. In addition,

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the publication removed the previous MAK (Maximale ArbeitsplatzKonzentrationen) and TRK (Technische Richtkonzentrationen) designations from substances. The current list is divided into Category I and II substances:

- Category I: substances for which the local effect has an assigned OEL or substances with a respiratory sensitizing effect.
- Category II: substances with a resorptive effect.

BAT values (Biologische Arbeitsstofftoleranzwerte - Biological Tolerance Values) are listed in TRGS 903.

Currently, nickel and nickel compounds are regulated as follows:

- Nickel as metallic nickel, nickel sulfide and sulfidic ores, nickel oxide, and nickel carbonate: 0.5 mg Ni/m³ (calculated as nickel in total dust).
- Nickel compounds in the form of inhalable droplets: 0.05 mg Ni/m³ (calculated as nickel in total dust).

Currently Germany has proposed changing the TRK for nickel as metallic nickel, nickel sulfide and sulfidic ores, nickel oxide, and nickel carbonate from 0.5 mg Ni/m³ (calculated as nickel in total dust) to 0.05 mg Ni/m³ (Table 9-1).

9.1.4 Japan

In Japan, the Ministry of Labor (MOL) is responsible for the safety and health of workers. Under the Ordinance on Prevention of Hazards due to Specified Chemical Substances, derived from the Industrial and Health Law, the

Ministry has listed nickel carbonyl as a hazardous substance. Employers are required to attend courses on the proper installation of ventilation systems to assure that nickel carbonyl concentrations do not exceed 0.007 mg Ni/m³.

Although there are no mandated standards for inorganic forms of nickel, the Japan Association of Industrial Health, a non-governmental organization, has recommended an OEL (eight-hour TWA) of 1.0 mg Ni/m³ for all forms of inorganic nickel. The Association's OEL recommendation for nickel carbonyl is the same as the MOL's.

9.1.5 United States (U.S.)

In the U.S., the federal Occupational Safety and Health Act (OSHAct) of 1970 created the Occupational Safety and Health Administration (OSHA) within the Department of Labor. The stated intent of the OSHAct is to "assure safe and healthful working." To this end, OSHA has promulgated a variety of health and safety regulations, among them the Air Contaminants Standard, which specifies eight-hour Time Weighted Average Permissible Exposure Limits (PELs) for many substances, including nickel and its compounds. The current PEL for nickel metal and for both water-soluble and -insoluble nickel compounds is 1.0 mg Ni/m³. The PEL for nickel carbonyl is 0.007 mg Ni/m³.

In 1989, OSHA reduced the PEL for soluble nickel compounds to 0.1 mg Ni/m³. However, in July 1992, the U.S. Eleventh Circuit Court of Appeals set aside and remanded the entire Air Contaminants Standard on the ground that OSHA's generic approach – dealing with over 400 chemicals, including nickel, in a single rule-making – effectively precluded OSHA from

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making the substance-specific findings of significant risk and the industry-specific findings of technological and economic feasibility that are required by the OSHA Act. The effect of the Court of Appeals decision was stayed while OSHA sought review in the Supreme Court. OSHA's efforts to secure Supreme Court review ended in March 1993, and the PEL for soluble nickel compounds reverted to a level of 1.0 mg Ni/m³, the same as the PEL for nickel metal and insoluble nickel compounds.

In the future, OSHA may seek to reinstate some or all of the PELs that were vacated by the Eleventh Circuit Court of Appeals. If so, the PEL for soluble nickel compounds would be reduced to 0.1 mg Ni/m³. It also is possible that, in the years ahead, OSHA may decide to review nickel and its compounds in a substance-specific proceeding and set a more comprehensive standard for occupational exposure to nickel and individual nickel compounds.

Individual states that have approved occupational health programs may set more stringent requirements than those set by the federal government if they are able to make certain showings. While most states generally follow the federal limits, some individual states which have received authority to implement their own occupational health programs have maintained a PEL of 0.1 mg Ni/m³ for soluble nickel compounds.

As mentioned above, some governments have directly based their OELs upon the ACGIH's TLVs; others. However, others have not adopted the ACGIH TLVs as evidenced by independent decisions reached by countries such as Germany, the U.K., and the U.S.. The ACGIH is a non-governmental organization of occupational health professionals and technical personnel in govern-

ment agencies and educational institutions. It publishes an annually updated document on exposure limits called the *Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs)*. As the ACGIH is not a "true" governmental body, its TLVs are not enforceable standards and employers are not legally obligated to meet the TLVs, unless specifically required to do so by local or national law.

Currently, the TLVs are 1.5 mg Ni/m³ for metallic nickel, 0.2 mg Ni/m³ for water-insoluble forms of inorganic nickel, and 0.1 mg Ni/m³ for water-soluble nickel forms and nickel subsulfide. The TLV for nickel carbonyl is 0.35 mg Ni/m³. These TLVs were adopted in 1998. In addition to new TLVs and carcinogen classifications, the ACGIH stated that the nickel compound TLVs would be based on the *Inhalable Particulate Fraction* instead of the "Total" *Particulate Fraction*. In response to comments regarding the differential sampling efficiency of inhalable and 'total' aerosol samplers, the ACGIH increases the TLVs that would have resulted for "total" nickel resulting in the final "inhalable" TLVs published in 1998 (Table 9-1).

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Table 9-1: Limit Values As Established By Major Standard-Setting Bodies					
Country/Body	Status of Standard	Values of Standards ¹ (mg Ni/m ³)			
		Metallic Nickel	Insoluble Nickel Species	Soluble Nickel Species	Nickel carbonyl
Argentina	Current	1.5	0.2 0.1 (sulfidic)	0.1	0.35
Austria	Current	0.05 ²	0.05 ²	0.05	0.05 (ml/m ³)
Australia	Current	1.0	1.0	0.1	0.12
Belgium	Current	1.0	1.0	0.1	0.12
Brazil	Current	NA ⁸	NA ⁸	NA ⁸	0.28
Canada – Ontario	Current	1.0 ¹⁶	0.2 ¹⁶ 0.1 (subsulfide) ¹⁶	0.1 ¹⁶	0.35 ¹⁶
Canada – Alberta	Current	1.0 [2 ⁷]	1.0 (sulfide roasting fume) [3 ⁷]	0.1 [0.3 ⁷]	0.12 [0.36 ⁷]
Canada – British Columbia	Current	0.05	0.05 0.1 (subsulfide) ¹⁶	0.05	0.002
Canada – Québec	Current	1.0	1.0	0.1	0.007
Chile	Current	0.8	0.8	0.08	NA ⁸
Denmark	Current	0.05	0.05	0.01	0.007
Finland	Current	1.0	0.1	0.1	0.007 [0.021 ⁷]
France	Current	1.0 (VME) ⁵	1.0	0.1	0.12
Germany	Under revision	0.5 ⁶ [2.0 ⁷]	0.5 ⁶ [2.0 ⁷]	0.05 ^{6,16} [0.2 ⁷]	[0.24 ⁷]
Greece	NA ⁸	NA ⁸	NA ⁸	NA ⁸	NA ⁸
Italy	Current	1.0	1.0	0.1	0.12
Japan	Under revision	1.0	NS ¹²	NS ¹²	0.007
Netherlands	Current	0.1	NS ¹²	0.1	0.35
New Zealand	Current	1.0	1.0 (sulfide roasting fume and dust)	0.1	0.12
Norway	Current	0.05	0.05	0.05	0.007
Portugal	Current	1.0	NS ¹²	0.1	0.12
South Africa	Current	0.5	0.5 0.1 (subsulfide)	0.1	[0.24 NA ⁸]
Spain	Current	1.0	0.2	0.1	0.12
Sweden	Current	0.5	0.1 0.01 (subsulfide)	0.1	0.007
United Kingdom	Current	0.5 (MEL) ^{9,10}	0.5	0.1 (MEL) ¹⁰	0.24 (OES) ^{7,11}
United States	Current ¹³	1.0 ¹⁴	1.0	1.0	0.007
(USA) ACGIH TLV 15 Non-Enforceable Standard	Current (1997)	1.5 ¹⁶	0.2 ¹⁶ 0.1 (subsulfide) ¹⁶	0.1 ¹⁶	0.1 ¹⁶

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Footnotes to Table 9-1

- ¹ 8-hour TWA (Time-Weighted Average) unless otherwise noted. All values refer to 'total' nickel unless otherwise noted.
- ² This TLV applies to nickel metal and alloys, nickel sulfide, sulfidic ores, oxidic nickel, and nickel carbonate in inhalable dust, as well as any nickel compound in the form of inhalable droplets.
- ³ Metallic nickel only.
- ⁴ NC = No change.
- ⁵ VME = Valeur Moyenne d'Exposition. The value of 1 mg/m³ applies to Ni carbonate, dihydroxide, subsulfide, monoxide, sulfide, trioxide and for other chemical forms non-otherwise specified such as 'insoluble Ni compounds' and Ni sulfide roasting fume and dust.
- ⁶ TRK (Technische Richtkonzentrationen)
- ⁷ STEL=15-minutes, short-term standard.
- ⁸ NA = Not available.
- ⁹ MEL = Maximum Exposure Limit.
- ¹⁰ This value is based on "total inhalable" aerosol as measured with the 7-hole sampler (UK HSE, 2000).
- ¹¹ OES = Occupational Exposure Standard.
- ¹² NS = No Standard.
- ¹³ In 1989, OSHA reduced the PEL for soluble nickel compounds to 0.1 mg Ni/m³. However, in July 1992, the U. S. Eleventh Circuit Court of Appeals set aside and remanded the entire Air Contaminants Standard on the ground that OSHA's generic approach dealing with over 400 chemicals, including nickel, in a single rulemaking effectively precluded OSHA from making the substance-specific findings of significant risk and the industry-specific findings of technological and economic feasibility that are required by the Occupational Safety and Health Act. Accordingly, the PEL for soluble nickel compounds reverted to a level of 1.0 mg Ni/m³, the same as the PEL for nickel metal and insoluble nickel compounds. The PEL for soluble nickel compounds may, however, be lower than 1.0 mg Ni/m³ in individual states that have obtained OSHA's approval.
- ¹⁴ PEL = Permissible exposure limit.
- ¹⁵ ACGIH = American Conference of Governmental Industrial Hygienists.
- ¹⁶ Based on the inhalable particulate fraction. In response to comments regarding the differential sampling efficiency of inhalable and 'total' aerosol samplers, the ACGIH proposed increases to the 1996 proposed TLV values during January, 1997. The new recommendations will be placed on the Notice of Intended Changes during the spring of 1997. The ACGIH has also proposed carcinogen classifications of A5 (Not suspected as a human carcinogen) for metallic nickel, A4 (Not classifiable as a human carcinogen) for soluble nickel, A1 (Confirmed human carcinogen) for insoluble nickel, A1 for nickel subsulfide, and no classification for nickel carbonyl.

9.1.6 Biological Limit Values

Biological indicators of nickel exposure are currently under study by several non-governmental bodies, including the American Conference of Governmental Industrial Hygienists (ACGIH) and the World Health Organization (WHO).

In 1990, the Maximale Arbeitsplatz-Konzentrationen Commission (MAK) in Germany established "EKAs" (exposure equivalents for carcinogenic materials) for nickel. Despite the generally recognized poor correlation between exposure and nickel concentrations in urine (Bernacki *et al.*, 1978; Høgetveit *et al.*, 1978; Morgan and Rouge, 1979; Raithel *et al.*, 1981; Aitio, 1984; IPCS, 1991), the MAK recommended an EKA of 50 µg Ni/L in urine as being equivalent to an airborne exposure of 0.5 mg Ni/m³. The 0.5 mg Ni/m³ level is the current maximum allowable concentration in Germany for water-insoluble forms of nickel.

9.2 Australia – Hazardous Materials

The Department of the Environment, Water, Heritage and the Arts administers and implements the Hazardous Waste (Regulation of Exports and Imports) Act 1989. The Act was developed to enable Australia to comply with specific obligations under the Basel Convention (Basel Convention on the Control of the Transboundary Movements of Hazardous Wastes and their disposal), a Convention set up to control the international movements of hazardous wastes.

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The main purpose of the Hazardous Waste Act is to regulate the export and import of hazardous waste to ensure that hazardous waste is disposed of safely so that human beings and the environment, both within and outside Australia, are protected from the harmful effects of the waste.

The original Act of 1989 only controlled movements of wastes that lacked financial value, usually destined for final disposal operations (for example, by incineration or landfill). In 1996, the Act was amended to include wastes that possess financial value, usually destined for recycling and recovery operations. These amendments enabled Australia to meet all of its obligations under the Basel Convention. The Act requires that a permit be obtained before hazardous waste is exported from Australia or imported into Australia. Additional information can be found at: <http://www.environment.gov.au/>

9.3 Canada – Hazardous Materials

The Workplace Hazardous Materials Information System (WHMIS) is designed to provide information from the supplier of controlled products intended for use in the workplace to the users of those materials in the workplace. The term “supplier” includes the manufacturer, the distributor and the importer.

WHMIS is implemented by federal and provincial legislation. The federal Hazardous Products Act imposes responsibilities on the supplier to provide specific hazard warning labels with symbols and MSDSs for materials meeting the hazard classification criteria. Those that meet the hazard criteria are known as “controlled products.” These responsibilities are imposed

as a condition of sale in, or importation into, Canada. The hazard criteria and specific requirements for hazard warning labels and MSDSs are established in the Controlled Product Regulations.

Employers must ensure that all containers of controlled products in the workplace are properly labeled, that MSDSs for these controlled products are readily available to workers, and that workers are trained to understand and use the information. In the case of nickel, these provisions apply not only to primary nickel products and to nickel compounds but to processed forms as well, such as plate and sheet. The aforementioned duties on employers are set out in occupational health and safety legislation enacted by the provinces and the territories and by the federal government for federal employees. More information can be found at: http://www.hc-sc.gc.ca/ewh-semt/occup-travail/whmis-simdut/index_e.html

Trade secret provisions are included in the Controlled Product Regulations and the Hazardous Materials Information Review Act.

9.4 European Union (EU) – Hazardous Materials

Classification and labeling of dangerous substances and preparations are legislated in a series of Directives derived from 67/548 EEC which had gone through numerous “Amendments” and “Adaptations to Technical Progress.” Under these Directives, a “chemical” was either a pure “substance,” such as pure nickel or a nickel compound or a “preparation,” such as nickel alloys. In the case of substances, certain classification procedures were applied in categorizing the “haz-

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ard” of a substance. In the case of preparations, limit concentrations of the hazardous substance contained in the preparation are imposed and the preparation is categorized by these limits.

On 18 December 2006 the Council of Ministers adopted a new EU regulatory framework for Registration, Evaluation, and Authorisation (and restriction) of Chemicals (REACH). The European Chemicals Bureau (ECB) has the responsibility of developing methodologies, tools and technical guidance needed for REACH through a number of REACH Implementation Projects (RIPs).

REACH entered into force on June 1st 2007 to streamline and improve the former legislative framework on chemicals in the European Union (EU). REACH places greater responsibility on industry to manage the risks that chemicals may pose to the health and the environment. In principle REACH applies to all chemicals: not only chemicals used in industrial processes, but also in day-to-day life (*e.g.*, cleaning products, paints).

REACH replaces more than 30 pieces of legislation with a single Regulation. Other legislation regulating chemicals (*e.g.*, cosmetics, detergents) or related legislation (*e.g.*, on health and safety of workers handling chemicals, product safety, construction products) that were not replaced by REACH will continue to be in force. REACH is intended not to overlap or conflict with the other chemical legislation.

REACH makes industry bear most responsibilities to manage the risks posed by chemicals and provide appropriate safety information to their users. The regulation also enables the European Union to take additional measures (*e.g.*, banning use) on substances considered “highly dangerous”

(*e.g.*, carcinogens, mutagens, or reproductive toxicants or CMRs). REACH also creates the European Chemicals Agency (ECHA) with a central coordination and implementation role in the overall process.

In essence, REACH requires all manufacturers and importers of chemicals to identify and manage risks linked to the substances they manufacture and market. For substances produced or imported in quantities of 1 ton or more per year per company, manufacturers and importers need to demonstrate that they have appropriately done so by means of a registration dossier submitted to the ECHA.

Once the registration dossier has been received, the Agency may check that it is compliant with the Regulation and will evaluate testing proposals to ensure that the assessment of the chemical substances will not result in unnecessary testing, especially on animals. Where appropriate, authorities may also select substances for a broader substance evaluation to further investigate substances of concern.

REACH includes an authorization system aiming to ensure that substances of very high concern are adequately controlled, and progressively substituted by safer substances or technologies or only used where there is an overall benefit for society of using the substance. These substances will be prioritized and over time included in Annex XIV. Once they are included, industry will have to submit applications to the Agency on authorization for continued use of these substances. In addition, EU authorities may impose restrictions on the manufacture, use or placing on the market of substances causing an unacceptable risk to human health or the environment.

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Manufacturers and importers must provide their downstream users with the risk information they need to use the substance safely. This will be done via the classification and labeling system and Safety Data Sheets (SDS), where needed. For more information go to: <http://ecb.jrc.it/reach/>

9.5 Japan – Hazardous Materials

Guidelines in Japan for labeling hazardous substances, preparing MSDSs and training workers which conform with the ILO Report on Safety in the Use of Chemicals at Work (1990) became effective in 1993. MSDSs became popular after the introduction of Product Liability Law in 1996. With the amendment of the Air Pollution Control Law in 1997, nickel compounds are listed in the priority list as potential hazardous air pollutants by the National Environmental Consultation Committee and the producers of nickel compounds are now requested to release hazard information to their users by providing MSDSs on their nickel containing products. In March, 1997, the Tokyo Metropolitan Government introduced the rule to reduce the emissions of hazardous chemical substances (including nickel metal and its compounds) to the environment. The producers of these substances in Tokyo are required to provide MSDSs to protect their customer's workers.

9.6 United States (U.S.) – Hazardous Materials

The purpose of OSHA's Hazard Communication Standard (29 CFR 1910.1200) is to ensure that the hazards of all chemicals produced in or imported into the U.S. are evaluated and that information concerning their hazards is transmitted to employers and employees. This transmittal of information is to be accomplished by means of comprehensive hazard communication programs, which are to include container labeling and other forms of warning, MSDSs, and employee training.

Chemical manufacturers or importers must assess the hazards of chemicals which they produce or import and provide hazard warning labels and MSDSs to employers. These provisions also apply to massive forms of metal unless they qualify as an exempt "article," *i.e.*, a manufactured item whose end use depends on its shape or design and which does not release or result in exposure to a hazardous chemical under normal conditions of use (29 CFR 1910.1200).

Employers must provide information to their employees about the hazardous chemicals to which they are exposed by means of a hazard communication program, hazard warning labels and other forms of warning, MSDSs, and information and training. Trade secret provisions are included in the standard.

For more information on hazard communication programs, readers are advised to contact their local authorities.

References

1. Abbracchio, M. P., Heck, J. D., Costa, M. (1982). The phagocytosis and transforming activity of crystalline metal sulfide particles are related to their negative surface charge. *Carcinogenesis* (London), 3, 175-180.
2. ACGIH (American Conference of Governmental Industrial Hygienists). (1998). Threshold limit values and biological exposure indices for chemical substances and physical agents. Cincinnati, OH, p.51.
3. Aitio, A. (1984). Biological monitoring of occupational exposure to nickel. In: Sunderman, F. W., Jr., *et al.*, eds. *Nickel in the Human Environment: Proceedings of a Joint Symposium, March 1983, Lyon, France*. Lyon, France: International Agency for Research on Cancer. (IARC Scientific Publication No. 53). pp. 497-505.
4. Åkesson, B., Skerfving, S. (1985). Exposure in welding of high nickel alloy. *Intern. Arch. Occup. Environ. Health* 56: 111-117.
5. Allenby, C. and Goodwin, B. (1983). Influence of detergent washing powders on minimal eliciting patch test concentrations of nickel and chromium. *Contact Dermatitis* 9, (6): 491-499.
6. Ambrose, A., Larson, P., Borzelleca, J., Hennigar, G. Jr. (1976). Long term toxicologic assessment of nickel in rats and dogs. *J. Food Sci. Technol.*, 13, 181-187.
7. American Conference of Governmental Industrial Hygienists (ACGIH). (1993-94). Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: ACGIH.
8. Amor, A. J. (1932). Toxicology of carbonyls. *J. Indust. Hyg.* 14: 216-221.
9. Andersen, A., Engeland, A., Berge, S.R., Norseth, T. (1996). Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup. Environ. Med.* 53:708-713.
10. Andersen, I. and Svenes, K. (1989). Determination of nickel in lung specimens of thirty-nine autopsied nickel workers. *Int Arch Occup Environ Health* 61:289-295.
11. Andersson, K., Elinder, C. G., Hogstedt, C., Kjellstrom, T., Spang, G. (1984). Mortality among cadmium and nickel-exposed workers in a Swedish battery factory. *Toxicol. Environ. Chem.* 9: 53-62.
12. Anttila, A., Pukkala, E., Aitio, A., Rantanen, T., Karjalainen, S. (1998). Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. *Int. Arch. Occup. Environ. Health* 71: 245-250.
13. Arena, V., Sussman, N., Redmond, C., *et al.* (1998). Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort. *J Occup Environ Med* 40(10):907-916.
14. Bagot M., Charue D., Flechet M.-L., Terki N., Toma A. and Revuz J. (1995) Oral desensitization in nickel allergy induces a decrease in nickel-specific T-cells. *Eur J Dermatol* 5, 614-617.
15. Baselt, R. (1980). *Biological Monitoring Methods for Industrial Chemicals*. Davis, California: Biomedical Publications. pp. 193-196.

References

16. Becker, N. (1999). Cancer mortality among arc welders exposed to fumes containing chromium and nickel. *JOEM* 41: 294-303.
17. Bennett, B. (1984). Environmental nickel pathways to man. In: Sunderman, F. W., Jr., *et al.*, eds. *Nickel in the Human Environment: Proceedings of a Joint Symposium*, March 1983, Lyon, France. Lyon, France: International Agency for Research on Cancer. (IARC Scientific Publication No. 53). pp. 487-492.
18. Benson, J., Burt, D., Carpenter, R., Eidson, A., Hahn, F., Haley, P., Hanson, R., Hobbs, C., Pickrell, J., Dunnick, J. (1988). Comparative inhalation toxicity of nickel sulfate to F344/N rats and B6C3F1 mice exposed for twelve days. *Fundam. Appl. Toxicol.*, 10, 164-178.
19. Benson, J., Burt, D., Cheng, Y., Hahn, F., Haley, P., Henderson, R., Hobbs, C., Pickrell, J., Dunnick, J. (1989). Biochemical response of rat and mouse lung to inhaled nickel compounds. *Toxicology* 57: 255-266.
20. Benson, J., Chang, I., Cheng, Y., Hahn, F., Kennedy, C., Barr, E., Maples, K., Snipes, M. (1995). Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate. *Fund. Appl. Toxicol.*, 28, 232-244.
21. Benson, J., Cheng, Y., Eidson, A., Hahn, F., Henderson, R., Pickrell, J. (1994). Time course of lesion development in F344/N rats subchronically exposed by inhalation to nickel subsulfide. Washington, DC: U. S. Department of Energy.
22. Benson, J., Henderson, R., McClellan, R., Hanson, R., Rebar, A. (1986). Comparative acute toxicity of four nickel compounds to F344 rat lung. *Fundam. Appl. Toxicol.*, 7, 340-347.
23. Benson, J., Carpenter, R., Hahn, F., Haley, P., Hanson, R., Hobbs, C., Pickrell, J., Dunnick, J.K. (1987). Comparative inhalation toxicity of nickel subsulfide to F344/N rats and B6C3F1 mice exposed for 12 days. *Fundam. Appl. Toxicol.* 9: 251-265.
24. Benson, J., March, T., Hahn, F., Seagrave, S., Divine, K., Belinsky, S. (2001). Short-term inhalation study with nickel compounds. Final report submitted to the Nickel Producers Environmental Research Association by Inhalation Toxicology Laboratory, Lovelace Respiratory Research Institute, Albuquerque, NM. August 2001. Available through NiPERA, Durham, NC.
25. Berge, S., Skyberg, K. (2001). Radiographic evidence of pulmonary fibrosis and possible etiologic factors at a nickel refinery in Norway. Report to the Nickel Producers Environmental Research Association, Durham, NC. Available through NiPERA, Durham, NC.
26. Berghem, L., Hansson, M., Lundborg, M., Camner, P. (1987). Fibronectin concentrations in lung lavage fluid after inhalation exposure to low levels of metals. *Environ. Res.* 43: 179-185.
27. Bernacki, E., Parsons, G., Roy, B., Mikc-Devic, M., Kennedy, C., Sunderman, F. Jr. (1978). Urine nickel concentrations in nickel-exposed workers. *Ann. Clin. Lab. Sci.* 8: 184-189.

References

28. Berry, J., Poupon, M., Judde, J., Galle, P. (1985). In vitro electron microprobe of carcinogenic nickel compound interaction with tumor cells. *Ann. Clin. Lab. Sci.* 15: 109-120.
29. Bingham, E., Barkley, W., Zerwas, M., Stemmer, K., Taylor, P. (1972). Responses of alveolar macrophages to metals. I. Inhalation of lead and nickel. *Arch. Environ. Health* 25: 406-414.
30. Bk Tox (1999). Position paper by the Toxicology Consultant's Group, BK Tox (Beraterkreis Toxikologie), submitted to the German committee on dangerous substances or AGS (Ausschuß für Gefahrstoffe) for the classification of nickel metal, nickel alloys and nickel compounds.
31. Block, G., and Yeung, M. (1982). Asthma induced by nickel. *JAMA J. Am. Med. Assoc.* 247:1600-1602.
32. Boysen, M., Solberg, L., Torjussen, W., Poppe, S., Høgetveit, A. (1984). Histological changes, rhinoscopic findings and nickel concentrations in plasma and urine in retired nickel workers. *Acta Otolaryngol* 97: 105-115.
33. Bright, P., Burge, P., O'Hickey, S., Gannon, P., Robertson, A., Boran, A. (1997). Occupational asthma due to chrome and nickel electroplating. *Thorax* 52: 28-32.
34. Broder, I., Smith, J., Corey, P., Holness, L. (1989). Health status and sulfur dioxide exposure of nickel smelter workers and civic laborers. *J. Occup. Med.* 31: 347-353.
35. Brown, S., Nomoto, S., Stoeppler, M., Sunderman, F. Jr. (1981). IUPAC reference method for analysis of nickel in serum and urine by electrothermal atomic absorption spectrophotometry. *Clin. Biochem.* 14: 295-299.
36. Casey, C. and Robinson, M. (1978). Copper, manganese, zinc, nickel, cadmium, and lead in human foetal tissues. *Br. J. Nutr.* 39: 639-646.
37. Cavelier, C., Foussereau, J., Gille, P., Zissu, D. (1989). Allergy to nickel or cobalt: Tolerance to nickel and cobalt samples in man and in the guinea pig allergic or sensitized to these metals. *Contact Dermatitis*, 21, 72-78.
38. Chashschin, V.P., Artunina, G.P., Norseth, T. (1994). Congenital defects, abortion and other health effects in nickel refinery workers. *Sci. Total Environ.* 148: 99-102.
39. Chen, C-Y., Lin, T-H. (1998). Nickel toxicity to human term placenta: in vitro study on lipid peroxidation. *J. Toxicol. Environ. Health* 54: 37-47.
40. Christensen, O. and Lagesson, V. (1981). Nickel concentrations of blood and urine after oral administration. *Ann Clin Lab Sci* 11:119-125.
41. Christensen, O., Moller, H., Andrasko, L., Lagesson, V. (1979). Nickel concentration of blood, urine and sweat after oral administration. *Contact Dermatitis* 5: 312-316.
42. Cohn, J. and Emmett, E. (1978). The excretion of trace metals in human sweat. *Ann. Clin. Lab. Sci.* 8: 270-275.
43. Cohrssen, J., Covello, V. (1989). Risk Analysis: A Guide to Principles and Methods for Analyzing Health and Environmental Risks. National Technical Information Services, Springfield, VA. NTIS Order No. PB 89-137772.

References

44. Comité Européen de Normalisation (CEN). (1994). General requirements for the performance of procedures for workplace measurements. Draft standard prEN482. Brussels, Belgium: Commission of European Communities.
45. Cooper, W. C., Wong, O. (1981). A study of mortality in a population of nickel miners and smelter workers in Oregon.
46. Cornell, R. (1984). Mortality patterns among stainless steel workers. In: Sunderman, F. W., Jr., ed. Nickel in the Human Environment: Proceedings of a Joint Symposium; March 1983; Lyon, France. Lyon, France: International Agency for Research on Cancer, (IARC Scientific Publication No. 53), pp. 65-71.
47. Costa, M. (1991). Molecular mechanisms of nickel carcinogenesis. *Ann. Rev. Pharmacol Toxicol.* 31: 321-37.
48. Costa, M., Mollenhauer, H. (1980a). Carcinogenic activity of particulate nickel compounds is proportional to their cellular uptake. *Science (Washington, DC)*, 209, 515-517.
49. Costa, M., Sutherland, J.E., Peng, W., Salnikow, K., Broday, L., Kluz, T. (2001) Molecular biology of nickel carcinogenesis. *Mol. Cell Biochem.* Jun;222(1-2):205.
50. Cox, J., Doll, R., Scott, W., Smith, S. (1981). Mortality of nickel workers: Experience of men working with metallic nickel. *Br. J. Ind. Med.* 38: 235-239.
51. Cragle, D., Hollis, D., Newport, T., Shy, C. (1984). A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant. In: Sunderman, F. W., Jr., ed. Nickel in the Human Environment: Proceedings of a Joint Symposium; March 1983; Lyon, France. Lyon, France: International Agency for Research on Cancer, (IARC Scientific Publication No. 53), pp. 57-63.
52. Creason, J., Svendsgaard, D., Bumgarner, J., Pinkerton, C., Hinners, T. (1976). Maternal-fetal tissue levels of 16 trace elements in 8 selected continental United States communities. In: Hemphill, D.D., ed. Trace Substances in Environmental Health-X: Proceedings of University of Missouri's 10th Annual Conference of Trace Substances in Environmental Health, Columbia, Missouri, pp. 53-62.
53. Cross, H., Beach, J., Levy, L., Sadhra, S., Sorahan, T., McRoy, C. (1999). Manufacture, processing and use of stainless steel: a review of the health effects. Commissioned by the European Confederation of Iron and Steel Industries (EUROFER), Bruxelles, Belgium, January 1999.
54. Davies, J. (1986). Occupational asthma caused by nickel salts. *J. Soc. Occup. Med.*, 36, 29-31.
55. Diamond, G., Goodrum, P., Felter, S., Ruoff, W. (1998). Gastrointestinal absorption of metals. *Drug Chem. Toxicol.* 21: 223-251.
56. Driscoll, K., Costa, D., Hatch, G., Henderson, R., Oberdörster, G., Salem, H., Schlesinger, R. B. (2000). Intratracheal instillation as an exposure technique for the evaluation of respiratory tract toxicity: uses and limitations. *Toxicol. Sciences* 55: 24-35.

References

57. Duffus, J. (1996). Epidemiology and the identification of metals as human carcinogens. *Sci. Prog.* 79(4): 311-326.
58. Dunnick, J., Benson, J., Hobbs, C., Hahn, F., Cheng, Y., Eidson, A. (1988). Comparative toxicity of nickel oxide, nickel sulfate hexahydrate, and nickel subsulfide after 12 days of inhalation exposure to F344/N rats and B6C3F1 mice. *Toxicology*, 50, 145-156.
59. Dunnick, J., Elwell, M., Benson, J., Hobbs, C., Hahn, F., Haley, P., Cheng, Y., Edison, A. (1989). Lung toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulfide or nickel sulfate hexahydrate in F344/N rats and B6C3F1 mice. *Fund. Appl. Toxicol.* 12: 584-594.
60. Easton, D., Peto, J., Morgan, L., Metcalfe, L., Usher, V., Doll, R. (1992). Respiratory cancer mortality in Welsh nickel refiners: which nickel compounds are responsible? In: Nieboer, E., Nriagu, J.O., eds. *Nickel and Human Health: Current Perspectives*. New York, NY: Wiley & Sons, Inc., pp. 603-619.
61. EC. European Commission. (1999). European Commission Communication of 20 July 1999, published in the Official Journal of the European Communities: Volume C 205, p5.
62. Edoute, Y., Vanhoutte, P., Rubanyi, G. (1992). Mechanisms of nickel-induced coronary vasoconstriction in isolated perfused rat hearts. In: Nieboer, E., Nriagu, J. O., eds. *Nickel and Human Health: Current Perspectives: Proceedings of the Fourth International Conference on Nickel Metabolism and Toxicology*, September 1988, Helsinki, Finland. New York, New York: John Wiley & Sons, Inc. pp. 587-602.
63. Egedahl, R., Carpenter, M., Lundell, D. (2001). Mortality experience among employees at a hydrometallurgical nickel refinery and fertiliser complex in Fort Saskatchewan, Alberta (1954-95) *Occup Environ Med* 58(11):711-715.
64. Egedahl, R., Fair, M., Homik, R. (1993). Mortality among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Alberta (1954-1984). *Can J Public Health* 84:40-44.
65. Eisler, R. (1998): Nickel hazards to fish, wildlife, and invertebrates: a synoptic review. US Geological Survey Contaminant Hazard Report No. 34. Biological Science Report USGS/BRD/BSR-1998-0001.
66. Emmett, E., Risby, T., Jiang, L., Ng, S., Feinman, S. (1988). Allergic contact dermatitis to nickel: Bioavailability from consumer products and provocation threshold. *J. Am. Acad. Dermatol.* 19: 314-322.
67. Enterline, P. and Marsh, G. (1982). Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. *J. Natl. Cancer Inst.* 68: 925-933.
68. Estlander, T., Kanerva, L., Tupasela, O., Keskinen, H., Jolanki, R. (1993). Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. *Clin. Exp. Allergy* 23: 306-310.
69. Eurometaux. (1993). Guide to Labelling of Toxic and Harmful Metals and Alloys

References

- When in Massive and Particulate Forms. Brussels, Belgium: Eurometaux. 9 pages.
70. Fischer, A. (1989). The cellular toxicity of nickel. *Life Chem. Rep.*, 7, 149-168.
 71. Fischer, T. (1989). Occupational nickel dermatitis. In: Maibach, H. I., Menné, T., eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, Florida: CRC Press. pp. 117-132.
 72. Foulkes, E. and McMullen, D. (1986). On the mechanism of nickel absorption in the rat jejunum. *Toxicology* 38: 5-42.
 73. Fullerton, A., Andersen, J., Hoelgaard, A., Menné, T. (1986). Permeation of nickel salts through human skin in vitro. *Contact Dermatitis* 15: 173-177.
 74. Gawkrödger, D. (1996). Nickel dermatitis: how much nickel is safe? *Contact Derm.* 35: 267-271.
 75. Gawkrödger, D. (2001). Biological monitoring program for nickel-exposed workers: dermatological aspects. Proceedings of a Workshop: Occupational Exposure and Health Assessment Guidelines for Nickel. Nickel Producers Environmental Research Association (NiPERA), April, 2001, London, U.K. CD ROM available through NiPERA, Durham, NC.
 76. Gerin, M., Fletcher, A., Gray, C., Winkelmann, R., Boffetta, P., Simonato, L. (1993). Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders. *Int. J. Epidemiol.*, 22: 22-28.
 77. Gerin, M., Simiatycki, J., Richardson, L., Pellerin, J., Lakhani, R., Dewar, R. (1984). Nickel and cancer associations from a multicancer occupation exposure case-referent study: Preliminary findings. In: Sunderman, F.W., Jr., ed. *Nickel in the Environment: Proceedings of a Joint Symposium*, March, 1983, Lyon, France. Lyon, France: International Agency for Research on Cancer. (IARC Scientific Publication No. 53). pp. 105-115.
 78. Goldberg, M., Goldberg, P., Leclerc, A., Chastang, J., Fuhrer, R., Brodeur, J., Segnan, N., Floch, J., Michel, G. (1987). Epidemiology of respiratory cancers related to nickel mining and refining in New Caledonia (1978-1984). *Int. J. Cancer*, 40, 300-304.
 79. Goldberg, M., Goldberg, P., Leclerc, A., Chastang, J., Marne, M., Gueziec, J., Lavigne, F., Dubourdieu, D., Huerre, M. (1992). A seven-year survey of respiratory cancers among nickel workers in New Caledonia (1978-1984). In: Nieboer, E. and Nriagu, J. O., eds. *Nickel and human health: Current perspectives*. New York, NY: John Wiley & Sons, Inc., pp. 649-657.
 80. Goutet, M., Ban, M., Binet, S. (2000). Effects of nickel sulfate on pulmonary immunity in Wistar rats. *Toxicology* 145: 15-26.
 81. Grandjean, P. (1984). Human exposure to nickel. In: Sunderman, F. W., Jr., *et al.*, eds. *Nickel in the Human Environment: Proceedings of a Joint Symposium*, March 1983, Lyon, France. Lyon, France: International Agency for Research on Cancer. (IARC Scientific Publication No. 53). pp. 469-480.

References

82. Grandjean, P., Nielson, G., Anderson, O. (1989). Human nickel exposure and chemobiokinetics. In: Maibach, H. E., Menné, T., eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, Florida: CRC Press. pp. 9-34.
83. Graney, J., Landis, M., Norris, G. (2004). Concentrations and solubility of metals from indoor and personal exposure PM_{2.5} samples. *Atmos Environ* 38(2):237-247.
84. Grimsrud, T., Berge, S., Resmann, F., Norseth, T., Andersen, A. (2000). Assessment of historical exposure in a nickel refinery in Norway. *Scand. J. Work Environ. Health*. 26(4): 338-345.
85. Grimsrud, T., Berge, S., Martinsen, J., *et al.* (2003). Lung cancer incidence among Norwegian nickelrefinery workers 1953-2000. *J Environ Monit* 5(2):190-197.
86. Grosjean, M. (1994). European standardization: guidance on the assessment of occupational exposure to chemical agents. *Analyst* 119: 9-12.
87. Haber, L., Diamond, G. L., Zhao, Q., Erdreich, L., Dourson, M. L. (2000b). Hazard identification and dose response of ingested nickel-soluble salts. *Reg. Toxicol. Pharm.* 31:231-241.
88. Haber, L., Erdreich, L., Diamond, G. L., Maier, A. M., Ratney, R.; Zhao, Q., Dourson, M. L. (2000a). Hazard identification and dose response of inhaled nickel-soluble salts. *Reg. Toxicol. Pharm.* 31: 210-230.
89. Hall, G. (2001). Occupational health aspects of lung cancer and monitoring of the workplace and the worker in nickel exposures. *Proceedings of a Workshop: Occupational Exposure and Health Assessment Guidelines for Nickel*. Nickel Producers Environmental Research Association (NiPERA), April, 2001, London, U.K. CD ROM available through NiPERA, Durham, NC.
90. Hall, S. (1989). Biological monitoring of metal exposure. *Pollut. Eng.* 1: 128-131.
91. Hansen, K., Lauritsen, J., Skytthe, A. (1996). Cancer incidence among mild steel and stainless steel welders and other metal workers. *Am. J. Ind. Med.* 30: 373-382.
92. Haudrechy, P., Foussereau, J., Mantout, B., Baroux, B. (1994). Nickel release from nickel plated metals and stainless steels. *Contact Derm.* 31: 249-255.
93. Heim, K., Bates, H., Rush, R., Oller, A. (2007). Oral Carcinogenicity Study with Nickel Sulfate Hexahydrate in Fischer 344 rats. *Toxicology and Applied Pharmacology* 224, 126-137.
94. Hemingway, J. and Molokhia, M. (1987). The dissolution of metallic nickel in artificial sweat. *Contact Dermatitis*, 16, 99-105.
95. Hindsén, M., Bruze, M., Christensen, O. (2001): Flare up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions, *J Am Acad Dermatol* 44. 616-23
96. Hirano, S., Shimada, T., Osugi, J., *et al.* (1994). Pulmonary clearance and inflammatory potency of intratracheally instilled or acutely inhaled nickel sulfate in rats. *Arch Toxicol* 68:548-554.
97. Høgetveit, A., Barton, R., Andersen, I. (1980). Variations of nickel in

References

- plasma and urine during the work period. *J. Occup. Med.* 22: 597-600.
98. Høgetveit, A., Barton, R., Kostøl, C. (1978). Plasma nickel as a primary index of exposure in nickel refining. *Ann. Occup. Hyg.* 21: 113-120.
 99. Hsieh, T., Yu, C., Oberdörster, G. (1999). Deposition and clearance models of Ni compounds in the mouse lung and comparisons with the rat models. *Aerosol Sci. Tech.* 31:359-372 (1999).
 100. Hueper, W. (1958). Experimental studies in metal cancerigenesis: IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalation of powdered metallic nickel. *AMA Arch. Pathol.*, 65, 600-607.
 101. Hueper, W. and Payne, W. (1962). Experimental studies in metal carcinogenesis. *Arch. Environ. Health*, 5, 445-462.
 102. IARC. International Agency for Research on Cancer. (1990). IARC monographs on the evaluation of carcinogenic risks to humans of chromium, nickel, and welding: v. 49. Geneva, Switzerland: World Health Organization. pp. 257-446.
 103. ICME. International Council on Metals and the Environment. (1999). Guide to Data Gathering Systems for Risk Assessment of Metals and Metal Compounds. Ottawa, Ontario, Canada. Available through the International Council on Mining and Metals, London, UK.
 104. ICNCM. International Committee on Nickel Carcinogenesis in Man. (1990). Report of the International Committee on nickel carcinogenesis in man. *Scand. J. Work Environ. Health* 16(1): 1-84.
 105. ILO. International Labour Organization. (1990). ILO Convention No. 170 – Safety in the Use of Chemicals at Work. ILO Official Bull. Series A No. 2 Vol. LXXIII. 9 p.
 106. International Committee on Nickel Carcinogenesis in Man (ICNCM). (1990). Report of the International Committee on Nickel Carcinogenesis in Man. *Scand J Work Environ Health* 16(1):1-82.
 107. International Standards Organisation (ISO). (1992). Air quality - particle size fraction definitions for health related sampling. Technical report no. ISO/TR/7708-1983. Geneva, Switzerland: International Standards Organisation.
 108. IPCS. International Programme on Chemical Safety. (1991). Environmental Health Criteria 108: Nickel. Geneva, Switzerland: World Health Organization. 383 p.
 109. Ishimatsu, S., Kawamoto, T., Matsuno, K., *et al.* (1995). Distribution of various nickel compounds in rat organs after oral administration. *Biol Trace Elem Res* 49(1):43-52.
 110. Jakobsson, K., Mikoczy, Z., Skerfving, S. (1997). Deaths and tumours among workers grinding stainless steel: a follow up study. *Occup. Environ. Med.* 54: 825-829.
 111. J rup, L., Bellander, T., Hogstedt, C., Spang, G. (1998). Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup. Environ. Med.* 55: 755-759.
 112. Joo, F. (1969). Changes in the molecular organization of the basement membrane after inhibition of adenosine

References

- triphosphate activity in the rat brain capillaries. *Cytobios.* 1: 289-301.
113. Jordan, W., King, S. (1979). Nickel feeding in nickel-sensitive patients with hand eczema. *J Am Acad Dermatol* 1:506-508.
114. Judde, J.G., Breillout, F., Clemenceau, C., Poupon, M.F., Jasmin, C. (1987). Inhibition of rat natural killer cell function by carcinogenic nickel compounds: preventive action of manganese. *JNCI* 78: 1185-1190.
115. Kasprzak, K., Gabryel, P., Jarczewska, K. (1983). Carcinogenicity of nickel(II) hydroxides and nickel(II) sulfates in Wistar rats and its relation to the in vitro dissolution rates. *Carcinogenesis* 4: 275-279.
116. Kerosuo, H.; Kullaa, A.; Kerosuo, E.; Kanerva, L.; Hensten-Pettersen, A. (1996). Nickel Allergy in Adolescents in Relation to Orthodontic Treatment and Piercing of Ears. *Am J Orthod. Dentofac. Orthoped.* 109: 148-154.
117. Kilburn, K.H., Warshaw, R., Boylen, C.T., Thornton, J.C., Hopfer, S.M., Sunderman, F.W., Jr., Finklea, J. (1990). Cross-shift and chronic effects of stainless steel welding related to internal dosimetry of chromium and nickel. *Am. J. Ind. Med.* 17: 607-615.
118. Kinney, P., Chillrud, S., Ramstrom, S., *et al.* (2002). Exposure to multiple air toxics in New York City. *Environ Health Perspect* 110 (Suppl 4):539-546.
119. Kirkpatrick, D. (2002). A 28-Day Inhalation Toxicity Study of Nickel Metal in Albino Rats (Study No. WIL-437001). WIL Research Laboratories, Inc., Ashland, Ohio.
120. Kirkpatrick, D. (2004). A 13-Week Inhalation Toxicity Study (with Recovery) of Nickel Metal in Albino Rats (Study No. WIL-437002). WIL Research Laboratories, Inc., Ashland, Ohio.
121. Kjellström, T., Friberg, L., Rahnster, B. (1979). Mortality and cancer morbidity among cadmium-exposed workers. *Environ. Health Perspectives.* 28: 199-204.
122. Kjuus, H., Skjaerven, R., Langård, S., Lien, J., Aamodt, T. (1986). A case-referent study of lung cancer, occupational exposures and smoking. *Scand. J. Work Environ. Health* 12: 193-202.
123. Kollmeier, H., Seemann, J., Muller, K., *et al.* (1987). Increased chromium and nickel content in lung tissue and bronchial carcinoma. *Am J Ind Med* 11:659-669.
124. Koutrakis, P., Briggs, S., Leaderer, B. (1992). Source apportionment of indoor aerosols in Suffolk and Onondaga Counties, New York. *Environ Sci Technol* 26:521-527.
125. Kyono, H., Kusaka, Y., Homma, K., Kubota, H., Endoichikawa, Y. (1992). Reversible lung lesions in rats due to short-term exposure or ultrafine cobalt particles. *Ind. Health* 30: 103-118.
126. Lammintausta, K. and Maibach, H. (1989). Clinical concepts in nickel testing. In: Maibach, H. I. and Menné, T., eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, Florida: CRC Press. pp. 91-99.
127. Lammintausta, K., Kalimo, K., Jansén, C. (1985). Experimental nickel sensitization in the guinea pig: Comparison of different protocols. *Contact Derm.* 12: 258-262.

References

128. Lauwerys, R. and Hoet, P. (1993). Biological monitoring of exposure to inorganic and organometallic substances: Nickel. Industrial chemical exposure: Guidelines for biological monitoring. 2nd ed. Boca Raton, FL: Lewis Publishers. pp. 82-85.
129. Lippmann, M. (1995). Exposure data needs in risk assessment and risk management: database information needs. *Appl. Occup. Environ. Hyg.* 10(4): 244-250.
130. Lyles, R. and Kupper, L. (1996). On strategies for comparing occupational exposure data to limits. *American Industrial Hygiene Association Journal*, 57: 6-15.
131. Malo, J., Cartier, A., Gagno, G., Evans, S., Dolovich, J. (1985). Isolated late asthmatic reaction due to nickel sulphate without antibodies to nickel. *Clin. Allergy*, 15, 95-99.
132. Malo, J., Cartier, A., Doepner, M., Nieboer, E., Evans, S., Dolovich, J. (1982). Occupational asthma caused by nickel sulfate. *J. Allergy Clin. Immunol.*, 69, 55-59.
133. Malten, K. (1981). Thoughts on irritant contact dermatitis. *Contact Dermatitis* 7: 238.
134. Mark, D., Vincent, J. (1986). A new personal sampler for airborne total dust in workplaces. *Ann. Occup. Hyg.*, 30, 89-102.
135. Mathur, A. (1984). Occupational dermatitis and absorption in a metal plater. *Contact Derm.* 10: page 530.
136. McConnell, L., Fink, J., Schlueter, D., Schmidt, M. Jr. (1973). Asthma caused by nickel sensitivity. *Ann. Intern. Med.*, 78, 888-890.
137. McGregor, D., Baan, R., Partensky, C., Rice, J., Wilbourn, J. (2000). Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies-a report of an IARC Monographs Programme Meeting. *Europ. J. Cancer* 36: 307-313.
138. McMillan, C. and Burrows, D. (1989). In vitro testing in nickel contact hypersensitivity. In: Maibach, H. I. and Menné, T., eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, Florida: CRC Press. pp. 79-90.
139. McNeely, M., Sunderman, F. Jr., Nechay, M., Levine, H. (1971). Abnormal concentrations of nickel in serum in cases of myocardial infarction, stroke, burns, hepatic cirrhosis, and uremia. *Clin. Chem. (Winston-Salem, NC)* 17: 1123-1128.
140. Medinsky, M., Benson, J., Hobbs, C. (1987). Lung clearance and disposition of ⁶³Ni in F344/N rats after intratracheal instillation of nickel sulfate solutions. *Environ. Res.* 43: 168-178.
141. Medinsky, M., Benson, J., Hobbs, C. (1987). Lung clearance and disposition of ⁶³Ni in F344/N rats after intratracheal instillation of nickel sulfate solutions. *Environ. Res.* 43: 168-178.
142. Menne, T., Christophersen, J., Green, A. (1989). Epidemiology of nickel dermatitis. In: Maibach HI, Menne T, eds. *Nickel and the skin: Immunology and toxicology*. Boca Raton, FL: CRC Press, Inc., 109-115.
143. Menné, T. and Maibach, H.I. (1987). Systemic contact allergy reactions. *Sem. Dermatol.* 6: 108-118.

References

144. Morgan, L. (1992). Problems in the toxicology, diagnosis, and treatment of nickel carbonyl poisoning. In: Neiboer, E. and Nriagu, J. O., eds. *Nickel and human health: Current perspectives*. New York, NY: John Wiley & Sons, Inc., pp. 261-271.
145. Morgan, L. and Rouge, P. (1979). A study into the correlation between atmospheric and biological monitoring of nickel in nickel refinery workers. *Ann. Occup. Hyg.* 22: 311-317.
146. Morgan, L. and Rouge, P. (1984). Biological monitoring in nickel refinery workers. In: Sunderman, F. W., Jr., *et al.*, eds. *Nickel in the Human Environment: Proceedings of a Joint Symposium*, March 1983, Lyon, France. Lyon, France: International Agency for Research on Cancer. (IARC Scientific Publication No. 53). pp. 507-520.
147. Moulin J., Clavel, T., Roy, D., Danaché, B., Marquis, N., Févotte, J., Fontana, J. (2000). Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int. Arch. Occup. Environ. Health* 73: 171-180.
148. Moulin J., Wild, P., Mantout, B., Fournier, M., Betz, M., Mur J., Smagghe G., Mur, J. M. (1993). Mortality from lung cancer and cardiovascular diseases among stainless steel producing workers. *Cancer Causes Control* 4: 75-81.
149. Moulin, J., Clavel, T., Roy, D., *et al.* (2000). Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int. Arch. Occup. Environ. Health* 73(3):171-80.
150. Muhle, H., Bellmann, B., Takenaka, S., Fuhst, R., Mohr, U., Pott, F. (1992). Chronic effects of intratracheally instilled nickel containing particles in hamsters. In: Neiboer, E., Nriagu, J.O., eds. *Nickel and Human Health: Current Perspectives*. New York, NY: Wiley & Sons, Inc., pp. 467-480.
151. Muir, D., Julian, J., Jadon, N., Roberts, R., Roos, J., Chan, J., Maehle, W., Morgan, W. K. C. (1993). Prevalence of small opacities in chest radiographs of nickel sinter plant workers. *Br. J. Ind. Med.*, 50, 428-431.
152. Muller, I., Wheeler, W., Gentleman, J., *et al.* (1983). Study of the mortality of Ontario miners, 1955-1977: Part 1. Toronto, Canada: Atomic Energy Control Board of Canada, Ontario Workmen's Compensation Board, Ontario Ministry of Labour.
153. Murthy, R., Barkley, W., Hollingsworth, L., Bingham, E. (1983). Enzymatic changes in alveolar macrophages of rats exposed to lead and nickel by inhalation. *J. Am. Coll. Toxicol.* 2: 193-199.
154. NAS. (2002). Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy of Sciences. <http://books.nap.edu/books/0309072794/html/521.html>. January 13, 2005.
155. Nickel Development Institute (NiDI) (1994). Safe use of nickel in the workplace. Nickel Development Institute.
156. Nickel Development Institute (NiDI). (1995). Internal analysis tables. Nickel Development Institute.

References

157. Nieboer, E. (1997). Reproductive and developmental health in relation to occupational exposure to nickel in the Kola Peninsula of Russia: A feasibility study. Final Report to Nickel Producers Environmental Research Association, Durham, North Carolina. Available through NiPERA, Durham, NC.
158. Nielsen, G. and Flyvholm, M. (1984). Risks of high nickel intake with diet. In: Sunderman, F. W., Jr.; *et al.*, eds. Nickel in the Human Environment: Proceedings of a Joint Symposium; March 1983; Lyon, France. Lyon, France: International Agency for Research on Cancer. (IARC Scientific Publication No. 53). pp. 333-338.
159. Nielsen, G., Jepson, L., Jorgensen, P., *et al.* (1990). Nickel-sensitive patients with vesicular hand eczema: Oral challenge with a diet naturally high in nickel. *Br J Dermatol* 122:299-308.
160. Nielsen, G., Søderberg, U., Jørgensen, P., Templeton, D., Rasmussen, S., Andersen, K., Grandjean, P. (1999): Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity. *Toxicol Appl Pharmacol* 154, 67-75.
161. Nielsen, G., Rohold, A., Andersen, K. (1992). Nickel contact sensitivity in the guinea pig. An efficient open application test method. *Acta. Derm. Venereol.* 72: 45-48.
162. Nielsen, N. and Menné, T. (1992): Allergic contact sensitization in an unselected Danish Population. The Glostrup Allergy Study, Denmark, *Acta Dermato-Venereol* 72: 456-460.
163. NIOSH. National Institute of Occupational Safety and Health. (1987). Guide to Industrial Respiratory Protection. DHHS (NIOSH) PB No. 87-116.
164. NIOSH. National Institute of Occupational Safety and Health. (1994). Method No. 7300: Elements. NIOSH Manual of Analytical Methods. 4th ed. Issue 2, 15 August 1994.
165. NIOSH. National Institute of Occupational Safety and Health. (1994). Method No. 8005: Elements in Blood or Tissue. NIOSH Manual of Analytical Methods. 4th ed. Issue 2, 15 August 1994.
166. NIOSH. National Institute of Occupational Safety and Health. (1994). Method No. 8310: Metals in Urine. NIOSH Manual of Analytical Methods. 4th ed. Issue 2, 15 August 1994.
167. NiPERA (1996). Occupational exposure limits: Criteria document for nickel and nickel compounds. Prepared for the European Commission, Directorate General V by the Nickel Producers Environmental Research Association. Available through NiPERA, Durham, NC.
168. NiPERA (2000). An Oral (Gavage) Two-Generation Reproduction Toxicity Study in Sprague-Dawley Rats with Nickel Sulfate Hexahydrate. Springborn Laboratories, Spencerville, Ohio, U.S.A.; Final Report No. 3472.4 as reported to the Nickel Producers Environmental Research Association, Durham, North Carolina, U.S.A. Available through NiPERA, Durham, NC.
169. Nomoto, S. (1974). Determination and pathophysiological study of

References

- nickel in humans and animals. II. Measurements of nickel in human tissues by atomic absorption spectrometry. *Shinshu. Igaku. Zasshi* 22: 39-44.
170. Novey, H., Habib, M., Wells, I. (1983). Asthma and IgE antibodies induced by chromium and nickel salts. *J. Allergy Clin. Immunol.*, 72, 407-412.
171. NTP. National Toxicology Program Technical Report. (1996a). Toxicology and Carcinogenesis Studies of Nickel Subsulfide in F344/N Rats and B6C3F1 Mice. NTP TR 453, NIH publication Series No. 96-3369.
172. NTP. National Toxicology Program Technical Report. (1996b). Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate in F344/N Rats and B6C3F1 Mice. NTP TR 454, NIH Publication Series No. 96-3370.
173. NTP. National Toxicology Program Technical Report. (1996c). Toxicology and Carcinogenesis Studies of Nickel Oxide in F344/N Rats and B6C3F1 Mice. NTP TR 451, NIH Publication Series No. 96-3363.
174. NTP. National Toxicology Program. (1998). Report on Carcinogens, 8th Edition. U.S. Department of Health and Human Services, p. 146.
175. O'Rourke, M., Van De Water P., Jin S, *et al.* (1999). Evaluations of primary metals from NHEXAS Arizona: distributions and preliminary exposures. *J Expo Anal Environ Epidemiol* 9:435-445
176. Oberdörster, G., Baggs, R., Finkelstein, J. (1995). Pulmonary retention and effects of inhaled NiO and Ni3S2 in rats and mice: indicators of maximum tolerated dose. *Ann. Clin. Lab. Sci.* 25: 441 (Abstract).
177. Oller, A. (2002). Respiratory carcinogenicity assessment of soluble nickel compounds. *Environ Health Perspect. Suppl* 110(5):841-844
178. Oller, A. R., Costa, M., Oberdörster, G. (1997). Carcinogenicity assessment of selected nickel compounds. *Toxicol. Appl. Pharmacol.* 143:152-166.
179. Oller, A.R. (2001). Assessment of respiratory carcinogenicity associated with exposure to nickel and its compounds. Proceedings of a Workshop: Occupational Exposure and Health Assessment Guidelines for Nickel. Nickel Producers Environmental Research Association (NiPERA), April, 2001, London, U.K. Available through NiPERA, Durham, NC.
180. Ottolenghi, A., Haseman, J., Payne, W., Falk, H., MacFarland, H. (1974). Inhalation studies of nickel sulfide in pulmonary carcinogenesis of rats. *J. Natl. Cancer Inst.*, 54, 1165-1172.
181. Pang, D., Burges, D., Sorahan, T. (1996). Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945-93. *Occup. Environ. Med.* 53:714-717.
182. Panzani, R., Schiavino, D., Nucera, E., Pellegrino, S., Fais, G., Schinco, G., Patriarca, G. (1995): Oral hyposensitization to nickel allergy: Preliminary clinical results. *Int. Arch. Allergy Immunol* 107: 251-254.
183. Pariser, H. (1993). End-Use of Nickel: 1980-1992. Xanten, Germany: Alloy Metals & Steel Market Research. 213 p.

References

184. Patriarca, M., Lyon, T., Fell, G. (1997). Nickel metabolism in humans investigated with an oral stable isotope. *Am J Clin Nutr* 66(3):616-621.
185. Pennington J. and Jones J. (1987). Molybdenum, nickel, cobalt, vanadium, and strontium in total diets. *J Am Diet Assoc* 87:1644-1650.
186. Peto, J., Cuckle, H., Doll, R., Hermon, C., Morgan, L. G. (1984). Respiratory cancer mortality of Welsh nickel refinery workers. In: Sunderman, F. W., Jr., ed. *Nickel in the Human Environment: Proceedings of a Joint Symposium, March 1983, Lyon, France*. Lyon, France: International Agency for Research on Cancer, (IARC Scientific Publications No. 53), pp. 37-46.
187. Polednak, A. (1981). Mortality among welders, including a group exposed to nickel oxides. *Arch Environ Health* 36:235-242.
188. Pott, F., Rippe, R., Roller, M., Csicsaky, M., Rosenbruch, M. (1992). Carcinogenicity of nickel compounds and nickel alloys in rats by intraperitoneal injection. In: Nieboer, E.; Nriagu, J. O., eds. *Nickel and Human Health: Current Perspectives*. New York, NY: John Wiley & Sons, Inc., pp. 491-502.
189. Pott, F., Ziem, U., Reiffer, F. J., Huth, F. Ernst, H., Mohr, U. (1987). Carcinogenicity studies on fibers, metal compounds, and some other dusts in rats. *Exp. Pathol.* 32: 129-152.
190. Raithel, H., Mayer, P., Schaller, K. H., Mohrmann, W., Weltle, Dr., Valentin, H. (1981). Untersuchungen zur Nickel – Exposition bei Beschäftigten in der Glas-Industrie. 1. Objektivierung und quantifizierung der externen und internen Nickel-Balastung [Investigations regarding the exposure to nickel of workers in the glass industry. 1. Objectification and quantification of the external and internal contamination]. *Zbl. Arbeitsmed.* Bd. 31: 332-339.
191. Raithel, H., Schaller, K., Mohrmann, W., Mayer, P., Henkels, U. (1982). Untersuchungen zur Ausscheidungskinetik von Nickel bei Beschäftigten in der Glas- und Galvanischen Industrie [Study of elimination kinetics of nickel during injury in the glass and electroplating industry]. In: Fließner, T. M., ed. *Bericht über die 22. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin [Report on the 22nd Anniversary of the German Society of Occupational Medicine]*. Stuttgart, Gentner. pp. 223-228.
192. Raithel, H., Schaller, K., Akslen, L., I. (1989). Analyses of chromium and nickel in human pulmonary tissue. Investigations in lung cancer patients and a control population under special consideration of medical expertise aspects. *Int Arch Occup Environ Health* 61:507-512.
193. Rappaport, S., Lyles, R., Kupper, L. (1995). An exposure- assessments strategy accounting for within- and between-worker sources of variability. *Ann. Occup. Hyg.*, 39, 469-495.
194. Redmond, C., Arena, V., Costantino, J., Trauth, J., Bass, G., LeGasse, A. (1994). High nickel alloys workers study update. Final report to the Nickel Producers Environmental Research Association, May, 20.

References

195. Redmond, C., Arena, V., Costantino, J., Trauth, J., Bass, G., LeGasse, A. (1995). Supplemental analysis of high nickel alloys workers. Supplemental report to the Nickel Producers Environmental Research Association, December 15.
196. Rendall, R., Phillips, J., Renton, K. (1994). Death following exposure to fine particulate nickel from a metal arc process. *Ann. Occup. Hyg.*, 38, 921-930.
197. Rezuze, W., Knight, J., Sunderman, F. Jr. (1987). Reference values for nickel concentrations in human tissue and bile. *Ann. J. Ind. Med.* 11: 419-426.
198. Richardson, G., in association with Garrett, R., Mitchell, I., Mah-Paulson, M., Hackbarth, T. (2001). Critical review on Natural Global and Regional emissions of six trace metals to the atmosphere. Report prepared for the International Zinc Organisation, the International Copper Association and the Nickel Producers Environmental Research Association. Risklogic Scientific Services Ltd. Final report, July, 2001
199. Roberts, R., Julian, J., Muir, D., Shannon, H. (1989). A study of mortality in workers engaged in the mining, smelting, and refining of nickel: II. Mortality from cancer of the respiratory tract and kidney. *Toxicol. Ind. Health* 5: 975-993.
200. Roberts, R., Julian, J., Sweezey, D., Muir, D., Shannon, H., Mastromatteo, E. (1989a). A study of mortality in workers engaged in the mining, smelting, and refining of nickel. I: Methodology and mortality by major cause groups. *Toxicol. Ind. Health*, 5, 957-974.
201. Roberts, R., Julian, J., Sweezey, D., Muir, D., Shannon, H., Mastromatteo, E. (1989b). A study of mortality in workers engaged in the mining, smelting, and refining of nickel. I: Methodology and mortality by major cause groups. *Toxicol. Ind. Health*, 5, 957-974.
202. Rohold, A., Nielsen, G., Andersen, K. (1991). Nickel sulphate-induced contact dermatitis in the guinea pig maximization test: A dose-response study. *Contact Derm.* 24: 35-39.
203. Sanford, W. and Nieboer, E. (1992). Renal toxicity of nickel in humans. In: Nieboer, E., Nriagu, J.O., eds. *Nickel and Human Health: Current Perspectives*. New York, NY: Wiley & Sons., Inc., pp. 123-134.
204. Sanford, W., Nieboer, E., Bach, P., Stace, N., Gregg, N., Dobrota, M. (1988). The renal clearance and toxicity of nickel. In: *Fourth International Conference of Nickel Metabolism and Toxicology*. Espoo, Finland, p. 17.
205. Santucci, B., Cristaudo, A., Cannistraci, C., Picardo, M. (1988): Nickel sensitivity: Effects of prolonged oral intake of the element. *Contact Dermatitis* 19: 202-205.
206. Santucci, B., Manna, F., Cannistraci, C., *et al.* (1994). Serum and urine concentrations in nickel-sensitive patients after prolonged oral administration. *Contact Dermatitis* 30:97-101.
207. Schroeder, H., Balassa, J., Vinton, W. (1964). Chromium, lead, cadmium, nickel and titanium in mice: effect on mortality, tumors and tissue levels. *J. Nutr.*, 83, 239-250.

References

208. Schroeder, H., Mitchener, M., Nason, A. (1974). Life-term effects of nickel in rats: Survival, tumors, interactions with trace elements and tissue levels. *J. Nutr.*, 104: 239-243.
209. Schroeder, W., Dobson, M., Kane, D., (1987). Toxic trace elements associated with airborne particulate matter: A review. *Air Pollut Control Assoc* 11:1267-1287.
210. Schubert, H., Berova, N., Czernielewski, A., Hegyl, E., Jirásek, L., Koháka, V., Korossy, S., Michailov, P., Nebenführer, L., Prater, E., Rothe, A., Rudzki, E., Stanski, L., Süß, E., Tarnick, M., Temesvári, E., Ziegler, V., Zschunke, E. (1987). Epidemiology of nickel allergy. *Contact Derm.* 16: 122-128.
211. Seemann, J., Wittig, P., Kollmeier, H., Rothe, G. (1985). Analytical measurements of Cd, Pb, Zn, Cr, and Ni in human tissues. *Lab. Med.* 9: 294-299.
212. Serita, F., Kyono, H., Seki, Y. (1999). Pulmonary clearance and lesions in rats after a single inhalation of ultrafine metallic nickel at dose levels comparable to the Threshold Limit Value. *Indust. Health* 37: 353-363.
213. Shi, Z. (1986). Acute nickel carbonyl poisoning: A report of 179 cases. *Br. J. Ind. Med.*, 43, 422-424.
214. Shirakawa, T., Kusaka, Y., Fujimura, N., Kato, M., Heki, S., Morimoto, K. (1990). Hard metal asthma: Cross immunological and respiratory reactivity between cobalt and nickel? *Thorax* 45: 267-271.
215. Simonato, L., Fletcher, A., Andersen, A., Anderson, K., Becker, N., Chang-Claude, J., Ferro, G., Gérin, M., Gray, C., Hansen, K., Kalliomäki, P., Kurppa, K., Långard, S., Merló, F., Moulin, J., Newhouse, M., Peto, J., Pukkala, E., Sjögren, B., Wild, P., Winkelmann, R., Saracci, R. (1991). A historical prospective study of European stainless steel, mild steel, and shipyard welders. *Br. J. Ind. Med.* 48:145-154.
216. Sjövall, P., Christensen, O., Möller, H. (1987) Oral hyposensitization in nickel allergy. *J Am. Acad. Dermatol.* 17: 774-778.
217. Sobaszek, A., Boulenguez, C., Frimat, P., Robin, R., Haguenoer, J.M., Edme, J. (2000). Acute respiratory effects of exposure to stainless steel and mild steel welding fumes. *JOEM* 42: 923-931.
218. Sobaszek, A., Edme, J., Boulenguez, C., Shirali, P., Mereau, M., Robin, H., Haguenoer, J.M. (1998). Respiratory symptoms and pulmonary function among stainless steel welders. *JOEM* 40: 223-229.
219. Solomons, N., Viteri, F., Shuler, T., Nielsen, F. (1982). Bioavailability of nickel in man: Effects of foods and chemically-defined dietary constituents on the absorption of inorganic nickel. *J. Nutr.* 112: 39-50.
220. Sorahan, T. (1987). Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946-84. *Br. J. Ind. Med.* 44: 803-809.
221. Sorahan, T., Waterhouse, J. (1983). Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. *Br. J. Ind. Med.* 40: 293-300.
222. Stoeppler, M. (1980), Analysis of nickel in biological materials and

References

- natural waters. In: Nriagu, J. O., ed Nickel in the environment. New York, NY: John Wiley & Sons; 661-821.
223. Sumino, K., Hayakawa, K., Shibata, T., Kitamura, S. (1975). Heavy metals in normal Japanese tissues. Arch. Environ. Health. 30: 487-494.
 224. Sunderman, F., Jr., Hopfer, S., Swenney, K., Marcus, A., Most, B., Creason, J. (1989). Nickel absorption and kinetics in human volunteers. Proc. Soc. Exp. Biol. Med. 191: 5-11.
 225. Sunderman, F. Jr, Dingle, B., Hopfer, S., *et al.* (1988). Acute nickel toxicity in electroplating workers who accidentally ingested a solution of nickel sulfate and nickel chloride. Am J Ind Med 14:257-266.
 226. Sunderman, F. Jr., Hopfer, S., Plowman, M., Knight, J. (1990). Carcinogenesis bioassays of nickel oxides and nickel-copper oxides by intramuscular administration to Fischer-344 rats. Res. Commun. Chem. Pathol. Pharmacol., 70, 103-113.
 227. Sunderman, F. and Donnelly, A. (1965). Studies of nickel carcinogenesis metastasizing pulmonary tumors in rats induced by the inhalation of nickel carbonyl. Am. J. Pathol., 46, 1027-1041.
 228. Sunderman, F. Jr. (1988). Biological activities of nickel oxides; Final Report of Phases II and IV. Durham, NC: Nickel Producers Environmental Research Association; NiPERA Contract No. 87-08.
 229. Sunderman, F. Jr. (1989b). Chemistry, analysis, and monitoring. In: Maibach, H. I. and Menné, T., eds. Nickel and the Skin: Immunology and Toxicology. Boca Raton, Florida: CRC Press. pp. 1-9.
 230. Sunderman, F. Jr., Aitio, A., Morgan, L., Norseth, T. (1986). Biological monitoring of nickel. Tox. Ind. Health. 2(1): 17-78.
 231. Sunderman, F. and Kincaid, J. (1954). Nickel poisoning: II. Studies on patients suffering from acute exposure to vapors of nickel carbonyl. JAMA J. Am. Med. Assoc., 155, 889-894.
 232. Sunderman, F. and Sunderman, F. Jr. (1958). Nickel poisoning: VIII. Dithiocarb: A new therapeutic agent for persons exposed to nickel carbonyl. Am. J. Med. Sci., 236, 26-31.
 233. Sunderman, F., Allpass, P., Mitchell, J., Baselt, R., Albert, D. (1979). Eye malformations in rats: induction by prenatal exposure to nickel carbonyl. Science 203: 550-553.
 234. Sunderman, F., Shen, S., Reid, M., Allpass, R. (1980). Teratogenicity and embryotoxicity of nickel carbonyl in Syrian hamsters. Teratog. Carcinog. Mutagen. 1: 223-233.
 235. Sunderman, F. Jr., Hopfer, S., Crisostomo, M., Stoeppler, M. (1986b). Rapid analysis of nickel in urine by electrothermal atomic absorption spectrophotometry. Ann. Clin. Lab. Sci., 16, 219-230.
 236. Sunderman, F., Jr. (1971). Effect of nickel carbonyl upon hepatic concentrations of adenosine triphosphate. Res. Comm. Chem. Path. Pharm. 2: 545-550.
 237. Sunderman, F., Jr. (1984). Carcinogenicity of nickel compounds in animals. . In: Sunderman, F., Jr., ed. Nickel in the Human Environment: Proceedings of a Joint Symposium, March 1983, Lyon, France. Lyon, France: International Agency

References

- for Research on Cancer, (IARC Scientific Publications No. 53), pp. 37-46.
238. Sunderman, F. Jr. (2001). Review: nasal toxicity, carcinogenicity and olfactory uptake of metals. *Ann. Clin. Lab. Sci.* 31: 3-24.
 239. Sunderman, F. Jr., Donnelly, A., West, B., Kincaid, J. (1959). Nickel poisoning: IX. Carcinogenesis in rats exposed to nickel carbonyl. *AMA Arch. Ind. Health* 20: 36-41.
 240. Sunderman, F. Jr., Horak, E. (1981). Biochemical indices of nephrotoxicity, exemplified by studies of nickel nephrotoxicity. In: Brown, S.S., Davies, D.S. eds. *Organ-Directed Toxicity*. Pergamon Press, Oxford, U.K. pp. 55-67.
 241. Sunderman, F. Jr., McCully, K., Hopfer, S. (1984). Association between erythrocytosis and renal cancers in rats following intrarenal injection of nickel compounds. *Carcinogenesis* 5: 1511-1517.
 242. Svenes, K. and Andersen, I. (1998). Distribution of nickel in lungs from former nickel workers. *Int Arch Occup Environ Health* 71(6):424-428.
 243. Svensson, B. G., Englander, V., Akesson, B., Attewell R., Skerfvieng S., Ericson, A., Möller, T. (1989). Death of tumors among workers grinding stainless steel. *Am. J. Ind. Med.* 15: 51-59.
 244. Tanaka, I., Horie, A., Haratake, J., *et al.* (1988). Lung burden of green nickel oxide aerosol and histopathological findings in rats after continuous inhalation. *Biol Trace Elem Res* 16:19-26.
 245. Tanaka, I., Ishimatsu, S., Matsuno, K., *et al.* (1985). Biological half time of deposited nickel oxide aerosol in rat lung by inhalation. *Biol Trace Element Res* 8:203-210.
 246. Tedeschi, R. and Sunderman, F. (1957). Nickel poisoning. V. The metabolism of nickel under normal conditions and after exposure to nickel carbonyl. *Arch Ind Health* 16:486-488.
 247. Thomas, K., Pellizzari, E., Berry, M. (1999). Population-based intakes and tap water concentrations for selected elements in the EPA Region V National Human Exposure Assessment Survey (NHEXAS). *J Expo Anal Environ Epidemiol* 9:402-413.
 248. Thomassen, Y., Nieboer, E., Ellingsen, D., Hetland, S., Norseth, T., Odland, J., Romanova, N., Chernova, S., Tchachtchine, V. (1999). Characterization of workers' exposure in a Russian nickel refinery. *J. Environ. Mon.* 1: 15-22.
 249. Thornhill, P. (2000). Properties of nickel oxide used in toxicological research: The importance of appropriate characterization. Final Report to the Nickel Producers Environmental Research Association, Durham, NC. Available through NiPERA, Durham, NC.
 250. Todd, D. and Burrows, D. (1989). Nickel allergy in relationship to previous oral and cutaneous nickel contact. *Ulster Med. J.* 58: 168-171.
 251. Torjussen, W. and Andersen, I. (1979). Nickel concentrations in nasal mucosa, plasma and urine in active and retired nickel workers. *Ann Clin Lab Sci* 9:289-298.

References

252. Tossavainen, A., Nurminen, M., Mutanen, P., Tola, S. (1980). Application of mathematical modeling for assessing the biological half-times of chromium and nickel in field studies. *Br. J. Ind. Med.* 37: 285-291.
253. Tsai, P., Vincent, J., Mark, D. (1996a). Semi-empirical model for the aspiration efficiencies of personal aerosol samplers of the type widely used in occupational hygiene. *Annals of Occupational Hygiene* 40: 113-133.
254. Tsai, P., Vincent, J., Wahl, G., Maldonado, G. (1995). Occupational exposure to inhalable aerosol in the primary nickel production industry. *Occup. Environ. Med.*, 52, 793-799.
255. Tsai, P., Werner, M., Vincent J., Maldonado, G. (1996b). Exposure to nickel-containing aerosols in two electroplating shops: comparison between inhalable and 'total' aerosol. *Applied Occupational and Environmental Hygiene* 11: 484-492.
256. Tsalev, D. and Zaprianov, Z. (1984). Atomic absorption spectrometry in occupational and environmental health practice, v. 1. Boca Raton, FL: CRC Press.
257. Turjanmaa, K. and Reunala, T. (1991). Contact urticaria to surgical and household rubber gloves. In: Menné, T. and Maibach, H. I., eds. *Exogenous Dermatoses: Environmental Dermatitis*. Boca Raton, Florida: CRC Press. pp. 317-326.
258. U. S. EPA. U. S. Environmental Protection Agency. (1986). *Health Assessment Document for Nickel and Nickel Compounds*. EPA/600/8-83/012FF. Washington, DC: U. S. Environmental Protection Agency. 466 p.
259. Uter, W., Fuchs, T., Hausser, M., Ippen, H. (1995). Patch test results with serial dilutions of nickel sulfate (with and without detergent), palladium chloride, and nickel and palladium metal plates. *Contact Derm.* 32: 135-142.
260. Vaktiskjold, A., Talykova, L., Chashchin, V., Nieboer, E., Thomassen, Y., Odland, J. (2006). Genital malformations in newborns of female nickel-refinery workers. *Scand J Work Environ Health.* 32(1):41-50.
261. Vaktiskjold, A., Talykova, L., Chashchin, V., Odland, J., and Nieboer E. (2007). Small-for-gestational-age newborns of female refinery workers exposed to nickel. *Intl J Occ Med Envir Health.* 20(4):327-338.
262. Vaktiskjold, A., Talykova, L., Chashchin, V., Odland, J., and Nieboer E. (2008a). Spontaneous abortions among nickel-exposed female refinery workers. *Intl J Envir Health Research* 18(2):99-115.
263. Vaktiskjold, A., Talykova, L., Chashchin, V., Odland, J., and Nieboer E. (2008b). Maternal nickel exposure and congenital musculoskeletal defects among nickel-exposed female refinery workers. Submitted for publication.
264. Valentine, R. and Fisher, G. (1984). Pulmonary clearance of intratracheally administered $^{63}\text{Ni}3\text{S}2$ in strain A/J mice. *Environ. Res.* 34: 328-334.
265. van der Burg, C., Bruynzeel, D., Vreeburg, K., von Blomberg, B., Scheper, R. (1986). Hand eczema in hairdressers and nurses: a prospective study. *Contact Derm.* 14, 275-279.
266. van Hoogstraten, I., Boos C., Boden D., von Blomberg M., Scheper R. J.,

References

- Kraal G. (1993). Oral induction of tolerance to nickel sensitization in mice. *J Invest. Dermatol.* 101: 26-31.
267. van Hoogstraten, I., Andersen, K., von Blomberg, B., Boden, D., Bruynzeel, D., Burrows, D., Camarasa, J., Doooms-Goossens, A., Kraal, G., Lahti, A., Menné, T., Rycroft, R., Shaw, S., Todd, D., Vreeburg, K., Wilkinson, J., Scheper, R. (1991a). Reduced frequency of nickel allergy upon oral nickel contact at an early age. *Clin. Exp. Immunol.* 85: 441-445.
268. van Hoogstraten, I., Andersen, K., von Blomberg, B., Boden, D., Bruynzeel, D., Burrows, D., Camarasa, J., Doooms-Goossens, A., Kraal, G., Lahti, A., Menné, T., Rycroft, R., Todd, D., Vreeburg, K., Wilkinson, J., Scheper, R. (1989). Preliminary results of a multicenter study on the incidence of nickel allergy in relationship to previous oral and cutaneous contacts. In: P. J. Frosch, A. Doooms-Goossens, J.-M. Lachapelle, R. J. G. Rycroft and R. J. Scheper, eds. *Current Topics in Contact Dermatitis*. Springer-Verlag, Berlin, pp. 178-183.
269. van Hoogstraten, I., Boden, D., von Blomberg, M., Kraal, G., Scheper, R. (1992). Persistent immune tolerance to nickel and chromium by oral administration prior to cutaneous sensitization. *J. Invest. Dermatol.* 99: 608-616.
270. van Hoogstraten, I., von Blomberg, B., Boden, D., Kraal, G., Scheper, R. (1991b). Effects of oral exposure to nickel or chromium on cutaneous sensitization. In: B. J. Vermeer, K. D. Wuepper, W. A. van Vloten, H. Baart de la Faille, J. G. van der Schroeff, eds. *Metabolic Disorders and Nutrition Correlated with Skin*. Karger, Basel, pp. 237-241.
271. Van Vlack, L. (1980). *The Oxides of Nickel*. New York, NY: International Nickel Company, Inc. Toronto, Canada.
272. Van Winkle, M., Scheff, P. (2001). Volatile organic compounds, polycyclic aromatic hydrocarbons and elements in the air of ten urban homes. *Indoor Air* 11:49-64.
273. vankovic, S., Zeller, W., Komitowski, D., Edler, L., Lehman, E, Frohlich, N. (1988). Different carcinogenicity of two nickel alloys following intratracheal instillation in hamster. *Schriftenreihe der Bundesanstalt für Arbeitsschutz, Dortmund*.
274. Veien, N. and Menne, T. (1990). Nickel contact allergy and a nickel-restricted diet. *Semin Dermatol.* 9(3):197-205.
275. Veien, N., Hattel, T., Justesen, O., *et al.* (1987). Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt. *Acta Derm Venereol* 67:321-325.
276. Verma, D., Julian, J., Muir, D. (1996). Infrastructure and systems for risk assessment and metal compounds on human health. Available through the International Council on Mining and Metals, London, UK.
277. Vincent, J. (1989). *Aerosol Sampling: Science and Practice*. Chichester, United Kingdom: John Wiley & Sons, Inc. 390 p.
278. Vreeburg, K., deGroot, K., von Blomberg, M., Scheper, R. (1984). Induction of immunological tolerance by oral administration of nickel and chromium. *J. Dent. Res.* 63: 124-128.

References

279. Vuopala, U., Huhti, E., Takkunen, J., Huikko, M. (1970). Nickel carbonyl poisoning: Report of 25 cases. *Ann. Clin. Res.*, 2, 214-222.
280. Vyskočil, A., Senft, V., Viau, C., Cížková, M., Kohout, J. (1994). Biochemical renal changes in workers exposed to soluble nickel compounds. *Human Exp. Toxicol.* 13: 257-261.
281. Wall, L. and Calnan, C. (1980). Occupational nickel dermatitis in the electroforming industry. *Contact Derm.* 6: 414-420.
282. Warner, R., Dorn, C., Blakeslee, J., Gerken, D., Gordon, J., Angrick, E. (1988). Zinc effects on nickel dermatitis in the guinea pig. *Contact Dermatitis*, 19, 98-108.
283. Werner, M., Thomassen, Y., Hetland, S., Norseth, T., Berge, S.R., Vincent, J.H. (1999). Correlation of urinary nickel excretion with observed retention model with workplace data. *Reg. Toxicol. Pharm.* 33:165-72.
287. Zatka, J., Warner, J., Maskery, D. (1992). Chemical speciation of nickel in airborne dusts: An analytical method and results of an interlaboratory test program. *Environ. Sci. Tech.* 26: 138-144.
288. Zhang, Q., Kusaka, Y., Sato, K. (1998). Differences in the extent of inflammation caused by intratracheal exposure to three ultrafine metals: role of free radicals. *J. Toxicol. Environ. Health* 53: 423-438.
289. Zissu, D., Cavelier, C., De Ceaurriz, J., (1987). Experimental sensitization of guinea pigs to nickel and patch testing with metal samples. *Food Chem. Toxicol.* 25: 83-85.
290. Zober, A., Kick, K., Schaller, K., Schellmann, B., Valentin, H. (1984a). Normal values of chromium and nickel in human lung, kidney, blood, and urine samples. *Zbl. Bakt. Hyg. I. Abt. Org. B.* 179: 80-95.
291. Zober, A., Weltle, D., Schaller, K. (1984). Untersuchungen zur Kinetik von Chrom and Nickel in biologischen Material während einwöchigen Lichtbogenschweißens mit Chrom-Nickel-Haltigen Zusatzwerkstoffen [Study of the kinetics of chromium and nickel in biological material during a week of arc welding using chromium-nickel-containing filler metals]. *Schweissen Schneiden.* 10: 461-464.
285. Wilkinson, D. and Wilkinson, J. (1989). Nickel allergy and hand eczema. In: Maibach, H. I., Menné, T., eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, Florida: CRC Press. pp. 133-164.
286. Yu, C., Hsieh, T., Oller, A., Oberdörster, G. (2001). Evaluation of the human Ni

Abbreviations and Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists	IPCS	International Programme on Chemical Safety
ATSDR	Agency for Toxic Substances and Disease Registry	ISO	International Organization for Standards
BEI	Biological Exposure Indices	IUPAC	International Union of Pure and Applied Chemistry
CFR	Code of Federal Regulations	kg	Kilogram
CHIP	Chemical (Hazard Information and Packaging) Regulations	L	Liter
cm ²	Centimeter squared	LOAEL	Lowest Observed Adverse Effect Level
COSHH	Control of Substances Hazardous to Health		
Disulfiram	Tetraethylthiuram disulfide	m ³	Meter cubed
Dithiocarb	Diethyldithiocarbamate	MAK	Maximale Arbeitsplatzkonzentrationen
DNA	Deoxyribonucleic acid	MEL	Maximum Exposure Limit
EEC	European Economic Community	mg	Milligram
EKA _s	Exposure equivalents for carcinogenic materials	MOL	Ministry of Labor
EPA	Environmental Protection Agency	MSDS	Material Safety Data Sheets
EU	European Union	ng	Nanogram
FeSO ₄	Iron sulfate	NiO	Nickel oxide
FEV _{1.0}	Forced expiratory volume in one second	Ni ₃ S ₂	Nickel subsulfide
FVC	Forced vital capacity	NiSO ₄	Nickel sulfate
g	Gram	NiSO ₄ • 6H ₂ O	Nickel sulfate hexahydrate
H ₂ SO ₄	Sulfuric acid	(Fe,Ni) _{1-x} S	Nickelferrous pyrrhotite
HEPA	High efficiency particulate air	(Ni,Fe) ₉ S ₈	Pentlandite
HSC	Health and Safety Commission	NiDI	Nickel Development Institute
HSE	Health and Safety Executive	NIOSH	National Institute for Occupational Safety and Health
IARC	International Agency for Research on Cancer	NiPERA	Nickel Producers Environmental Research Association
ICNCM	International Committee on Nickel Carcinogenesis in Man	NOAEL	No Observed Adverse Effect Level
ILO	International Labour Organization	NOHSC	National Occupational Health and Safety Commission
		NTP	National Toxicology Program
		OEL	Occupational Exposure Limit
		OES	Occupational Exposure Standard

Abbreviations and Acronyms

OSHA	Occupational Safety and Health Administration
OSHAct	Occupational Safety and Health Act
PAHs	Polycyclic aromatic hydrocarbons
PEL	Permissible Exposure Limit
PPE	Personal Protective Equipment
SCBA	Self-Contained Breathing Apparatus
SMR	Standardized Mortality Ratio
TRK	Technische Richtkonzentrationen
TVL	Threshold Limit Value
TWA	Time-Weighted Average
TWAEAC	Time-Weighted Average Exposure Concentration
TWAEVs	Time-Weighted Average Exposure Values
µg	Microgram
µm	Micron
µM	Micromolar
U.K.	United Kingdom
U.S.	United States
WHMIS	Workplace Hazardous Materials Information System
WHO	World Health Organization
Wt%	Weight Percent

Appendix A – Sources of Useful Information

American Conference of Governmental Industrial Hygienists

1330 Kemper Meadow Drive
Cincinnati, Ohio 45240
U.S.A.
Customers/Members Telephone:
1 513 742 2020
Administrative Phone: 1 513 742 6163
Fax: 1 513 742 3355
Email: mail@acgih.org

American Industrial Hygiene Association

2700 Prosperity Avenue, Suite 250
Fairfax, Virginia 22031-4319
U.S.A.
Telephone: 1 703 849 8888
Fax: 1 703 207 3561
Email: infonet@aiha.org

American National Standards Institute

25 West 43rd Street, 4th Floor
New York, New York 10036
U.S.A.
Telephone: 1 212 642 4900
Fax: 1 212 398 0023

BSI British Standards

389 Chiswick High Road
London
W4 4AL
United Kingdom
Telephone: 44 (0)20 8996 9001
Fax: 44 (0)20 896 7001

Commission of the European Communities Directorate-General

Employment, Social Affairs and Education Health and Safety Directorate V/E

Bâtiment Jean Monnet
Rue Alcide de Gasperi
L-2920 Luxembourg
Grand Duchy of Luxembourg
Telephone: 352 4301 32015
Fax: 352 4301 30359
Email: PHEA@ec.europa.eu

Health and Safety Executive

Broad Lane
Sheffield S3 7HQ
United Kingdom
Telephone: 44 114 289 2606
Fax: 44 114 289 2850
Email: Lkenny@hsl.gov.uk

International Labour Organization

International Occupational Safety and Health Information Centre

CH-1211 Geneva 22
Switzerland
Telephone: 41 (0) 22 799 6111
Fax: 41 (0) 22 798 8685
Email: ilo@ilo.org

International Occupational Hygiene Association

Principle Office and Secretariat-British Occupational Hygiene Society

5/6 Melbourne Business Court, Millennium Way
Pride Park Derby
United Kingdom
DE24 8LZ
Telephone: 44 1332 298101
Fax: 44 1332 298099
Email: admin@ioha.net

Appendix A – Sources of Useful Information

International Organization for Standardization (ISO)

1, ch. De la Voie-Creuse,
Case postale 56
CH-1121 Geneva 20
Switzerland
Telephone: 41 22 749 01 11
Fax: 41 22 733 34 30

International Union of Pure and Applied Chemistry

IUPAC Secretariat

PO Box 13757
Research Triangle Park, NC 27709-3757
USA
Telephone: 1 919 485 8700
Fax: 1 919 485 8706

Japanese Ministry of Labor Labor Health and Safety

1-2-2 Kasumigaseki
Chiyoda-ku, Tokyo 100-8916
Japan
Telephone: 03-5253-1111
Fax: 81 3 3502 1598

Maximale Arbeitsplatz Konzentrationen Commission

Kennedyalle 40
D-53175 Bonn
Germany
Telephone: 49 228 8 85 1
Fax: 49 228 8 85 22 21

National Institute for Occupational Safety and Health

Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, Ohio 45226-1998
Mail Stop C22
U.S.A.
Telephone: 1 513 533 8462
Fax: 1 513 533 8573

National Occupational Health and Safety Commission (Worksafe Australia)

GPO Box 58
Sydney NSW 2001
Australia
Telephone: 61 2 565 9500
Fax: 61 2 565 9205

Nickel Institute

55 University Ave., Suite 1801
Toronto, Ontario M5J 2H7
Canada
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Fax: 1 416 591 7987

Nickel Producers Environmental Research Association

2605 Meridian Parkway, Suite 200
Durham, NC 27713
U.S.A.
Telephone: 1 919 544 7722
Fax: 1 919 544 7724

Appendix A – Sources of Useful Information

U.S. Department of Labor (Domestic Only)
Occupational Safety and Health Administration

200 Constitution Avenue
Washington, DC 20210

or

U.S. Department of Labor (International)
Occupational Safety and Health Administration for Internal Affairs
Occupational Safety & Health Administration

Room N3641
Washington, DC 20210
Telephone: 1 202 219 8148
Fax: 1 202 219 5986

Ontario Ministry of Labour

400 University Avenue
14th Floor
Toronto, Ontario M7A 1T7
Canada
Telephone: 1 416 326 7606
Fax: 1 416 326 0507

World Health Organization
International Programme on Chemical Safety

Avenue 20 Appia
CH-1211 Geneva 27
Switzerland
Telephone: 41 22 791 2111
Fax: 41 22 791 3111

Appendix B – Calculating Exposure Concentrations

Calculating Exposure Concentrations

In order to calculate the concentration of particulate, the sampled volume of air must be determined. The volume is determined by taking the average of the volumetric flowrates from the pump pre- and post-calibration and multiplying it by the time sampled. Corrections to the volume for any difference in air temperature or pressure between the area where calibration is performed and the area where air is sampled should be made using the ideal gas laws:

$$V_2 = \frac{T_2}{T_1} \times \frac{P_1}{P_2} \times V_1$$

where:

P_1 and T_1 are the conditions during calibration in units of mmHg and K, and P_2 and T_2 are the sampling conditions. V_1 is the calculated sample volume, and V_2 is the corrected volume.

From the laboratory analysis, which reports the mass of the contaminant collected, the concentration is calculated by dividing the mass of contaminant by the volume of air sampled:

$$C_n = \frac{\text{mass}_n \text{ (mg)}}{\text{volume}_n \text{ (m}^3\text{)}}$$

Calculating the Time-Weighted Average Exposure Concentration (TWAEC)

An employee's TWAEC is calculated by taking the sum of the products of the analytically-determined concentration (see above) for each sampling period and the duration of the corresponding sampling period and dividing this sum by the total sampling time as shown below:

$$\frac{C_1 T_1 + C_2 T_2 + \dots + C_n T_n}{T_1 + T_2 + \dots + T_n}$$

where:

C_n = concentration for sample n in mg/m³, and
 T_n = sampling time for sample n in minutes

It usually happens that the total sampling time is less than eight hours. If the TWAEC is to be compared with an eight-hour TWA standard such as the TLV, the calculated TWAEC must be adjusted to an eight-hour basis. This can be done by adding one or more $C_{ui} T_{ui}$ products to the numerator of the above equation and increasing the denominator to 480. As the added $C_{ui} T_{ui}$ product(s) refers to periods during which sampling was **not** conducted, estimates of C_{ui} must be made. If the person conducting the sampling decides that no exposure occurred during an unsampled period, the C_{ui} for that period would be set to zero.



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