NiPERA INC.
Nickel Producers Environmental Research Association

June 2, 2000

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson,

The enclosed comments on nickel metal and nickel alloys are submitted by the Nickel Producers Environmental Research Association (NiPERA) in response to NTP's request for information relevant to evaluating the potential human carcinogenicity of these substances (65 Fed. Reg. 17889, April 5, 2000). The Nickel Development Institute (NiDI)—in conjunction with Inco United States, Inc.—will be submitting a separate set of comments on the nomination of nickel metal and nickel alloys for possible listing in the 10th Report on Carcinogens (10th RoC).

During its deliberations on the 9th RoC, NTP initially considered listing *Nickel and All Nickel Compounds* as "*known human carcinogens*" but decided to focus solely on the listing of nickel compounds, putting metallic nickel off until the 10th RoC. Ultimately, the decision on listing nickel compounds also was deferred until the 10th RoC, so that nickel metal, nickel alloys, and the various nickel compounds could be addressed at one time. Thus, the 9th RoC maintains the listing of *Nickel and Certain Nickel Compounds* as substances that are "*reasonably anticipated to be a carcinogen.*"

In 1998, NiPERA submitted two sets of comments on NTP's proposal to list *All Nickel Compounds* as "*known human carcinogens.*" We pointed out that the proposal failed to recognize the critical importance of speciation in evaluating the toxicity and potential carcinogenicity of the various forms of nickel. Each compound or species of a metal, like nickel, has its own physico-chemical properties that dictate how it behaves under a given set of conditions, including interactions with biological organisms. Thus, the fact that one form of nickel may be carcinogenic via a particular route of exposure (*e.g.*, nickel subsulfide by inhalation) does not mean that a second nickel species (*e.g.*, nickel sulfate hexahydrate) also will be carcinogenic or that the first nickel species will be carcinogenic via a different route of exposure (*e.g.*, ingestion). This observation holds true not only for nickel compounds, but for nickel metal and nickel alloys as well. The different physico-chemical properties of various forms of the metal will largely determine the extent to which the free metal ion can be made bioavailable and delivered to a relevant biological site (*e.g.*, the nucleus of a lung epithelial cell).

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As we discussed in our 1998 comments, examination of the *in vitro*, animal, and epidemiological data pertaining to commercially relevant nickel compounds[1] indicates that these compounds have very different biological behaviors, particularly with regard to respiratory carcinogenicity. Nickel subsulfide is likely to be carcinogenic to humans. Soluble nickel compounds, by themselves, are not likely to be carcinogenic to humans, although an enhancing (promoter) effect on other carcinogens is possible. High concentrations of certain oxidic nickel mixtures (*i.e.*, Ni-Cu oxides mixed with low-temperature [black] and high-temperature [green] NiO) appear to be carcinogenic in epidemiological studies of nickel refinery workers. By contrast, exposures to nickel silicates-oxides and complex nickel oxides devoid of copper have not resulted in excess cancer risks in other human cohorts.

NiPERA and NiDI have identified a number of scientific issues that we believe need to be considered in evaluating the potential listing of all the above mentioned categories of nickel compounds, as well as metallic nickel and nickel alloys, in the 10th RoC. These issues are enumerated in an attachment to this letter.

NiPERA believes that—just as the different types of nickel compounds must be considered separately—separate carcinogenic assessments are needed for metallic nickel and for nickel-containing alloys since nickel alloys have their own special physico-chemical and biological properties that differ from those of their individual metal constituents. The enclosed comments are organized to reflect this important dichotomy.

While we discuss nickel metal and nickel alloys separately, we reach the same conclusion in each case—*i.e.*, occupational and general population exposures to metallic nickel and nickel alloys do not appear to pose a cancer risk for humans by relevant routes of exposure. Accordingly, we believe that nickel alloys should not be listed in the 10th RoC at all and that the listing of metallic nickel as "*reasonably anticipated to be a human carcinogen*" should be deleted.

We look forward to commenting further on these issues—and to providing additional information and perspective on the classification of nickel compounds—as NTP's consideration of the nickel-related listing proposals proceeds. If you have any questions about the enclosed comments, please contact me.

Sincerely,

Adriana R. Oller, Ph.D., DABT
Director of Research

Enclosure

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[1] For these purposes, we group the commercially relevant forms of nickel as follows: metallic nickel, oxidic nickel (including nickel oxides, hydroxides, silicates, carbonates, and complex nickel oxides), sulfidic nickel (including nickel sulfide and subsulfide), water soluble nickel compounds (including hydrated forms of nickel acetate, sulfate, chloride, *etc.*), and nickel carbonyl. Metallic nickel, oxidic and sulfidic nickel compounds, and nickel carbonyl are insoluble in water.

Important Scientific Issues Relevant for the Possible Listing of Nickel Metal, Nickel Alloys and Main Categories of Nickel Compounds in the Tenth RoC

The following are among the significant scientific issues that need to be considered in determining whether nickel metal, nickel alloys, and/or main categories of nickel compounds should be listed in the 10th RoC.

1. Different nickel species have different physicochemical properties that affect the bioavailability of the Ni^{2+} ion in different environmental and biological media and the ability of the Ni^{2+} ion to become available at a relevant biological site, such as the nucleus of a lung epithelial cell.

2. Different nickel species exhibit different toxicological properties in epidemiological and animal studies and in *in vitro* tests.

3. Each type of nickel alloy is a unique substance with its own special physicochemical and biological properties that differ from those of its individual metal constituents. The potential carcinogenicity of the principal categories of nickel alloys must, therefore, be evaluated separately from the potential carcinogenicity of nickel metal itself.

4. The most likely mechanism of nickel-related respiratory carcinogenicity suggests that some nickel species (*i.e.*, nickel subsulfide and, to a lesser extent, certain forms of oxidic nickel) are far more likely to be respiratory carcinogens than other forms of nickel (*i.e.*, metallic nickel, nickel alloys, and water soluble nickel compounds).

5. Animal evidence and mechanistic considerations indicate that soluble nickel compounds are more likely to have played an enhancing role, rather than acting as direct carcinogens, in epidemiological studies where an increased risk of respiratory cancer was found in certain cohorts within the nickel-producing industry.

6. Most epidemiological studies of workers in the nickel-producing and nickel-using industries are characterized by confounding exposures to a variety of nickel species and/or to other agents that are known to be respiratory carcinogens. In the 9th RoC, for example, NTP itself recently identified one such agent, *Strong Inorganic Acid Mists Containing Sulfuric Acid*, as a "Known Human Carcinogen." (This issue is of relevance mainly for evaluating the potential carcinogenicity of the various nickel compounds, since epidemiological studies have produced no evidence suggesting a causal association between exposure to metallic nickel or nickel alloys and increased respiratory cancer risk.)

7. The routes by which persons residing in the United States are exposed to nickel metal, nickel alloys, and the various nickel compounds differ. For water soluble nickel compounds, the principal routes of exposure will be inhalation and ingestion—with ingestion being far and away the primary source of exposure for the general population. For oxidic forms of nickel, inhalation will be the principal route of exposure. Exposure to sulfidic forms of nickel in the United States is negligible; to the extent it occurs, those exposures are through inhalation. By contrast, for the vast majority of the U.S. population, dermal contact is the only significant route of human exposure to metallic nickel—which is not present in food or drinking water and constitutes a negligible portion of the nickel present in ambient air. Even in occupational contexts, inhalation exposure

to metallic nickel is minimal, with certain exceptions (notably, nickel powder metallurgy operations and, to a lesser extent, nickel-battery manufacturing, and catalyst production). Dermal contact also is the principal route of exposure to nickel alloys, supplemented in special cases by exposure through prosthetic implants and dental appliances.

8. The points outlined in paragraph 7 above are particularly important because nickel-related carcinogenicity appears to be route-specific, as well as species-specific. Thus, a nickel species that is tumorigenic via one route of exposure (*e.g.*, injection) should not be presumed to present a carcinogenic risk via other routes of exposure. Accordingly, studies involving relevant routes of exposure to humans should be emphasized in evaluating the potential human carcinogenicity of the various nickel species.

9. In making carcinogenicity determinations for nickel metal, nickel alloys, and various categories of nickel compounds, a weight-of-the-evidence approach must be followed. Among other things, consideration must be given to:

    - Likely explanations for apparent discrepancies in the results of different epidemiological studies—*e.g.*, differences in the principal nickel species to which the workers were exposed, differences in levels of exposure, differences in possible confounding factors like smoking or the presence of other occupational carcinogens, etc.

    - The relevance of the routes of exposure used in animal studies—with greater emphasis being placed on results from studies employing routes of administration that are of relevance to human exposure scenarios.

    - The likely mechanism of action for nickel-related carcinogenesis and the implications that this may have for whether a particular nickel species is potentially a direct-acting carcinogen or, at most, an agent that may enhance an organism's response to exposure to other carcinogenic agents.

Comments of the Nickel Producers Environmental Research Association on the National Toxicology Program Proposal to List Metallic Nickel and Nickel-Containing Alloys in the Tenth RoC

June 2, 2000

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1. INTRODUCTION

The U.S. National Toxicology Program (NTP) is reviewing the database on the potential carcinogenicity of metallic nickel and nickel-containing alloys for possible listing of those substances in the 10th Report on Carcinogens (RoC). With regard to nickel alloys, it should be noted that 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. An alloy is a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. For example, 316L stainless steel is an alloy that contains approximately 18% chromium, 12% nickel, 3% molybdenum and ~70% iron, but particles of this alloy do not have the same physico-chemical and biological properties as a dust composed of 18% metallic chromium, 12% metallic nickel, 3% molybdenum, and 70% metallic iron particles. The potential carcinogenicity of nickel alloys must, therefore, be evaluated separately from the potential carcinogenicity of nickel metal itself. That is the approach we have followed in these comments, and we believe NTP should do so as well.

As discussed in Part 1 below, the weight of the evidence clearly does not support listing metallic nickel as a "*known human carcinogen*." In fact, it does not even justify listing nickel metal as "*reasonably anticipated to be a human carcinogen*." Accordingly, we urge that nickel metal be deleted from the list of "*reasonably anticipated human carcinogens*" when the 10th RoC is issued.

As discussed in Part 2 below, the weight of the evidence does not support listing nickel alloys as a "*known*" or "*reasonably anticipated*" human carcinogen either. Accordingly, nickel-containing alloys should not be listed in the 10th RoC at all.

2. METALLIC NICKEL

2.1 ROUTE OF EXPOSURE

Persons living in the United States can be exposed to particles of metallic nickel through inhalation, oral and dermal routes, and to massive forms of nickel metal through dermal exposure only.

2.1.1 Inhalation Exposure

2.1.1.1 Ambient air

Nickel is a ubiquitous trace element occurring in soil, water, air, and in the biosphere. On the basis of measured size distributions and vapor pressure data, it has been stated that the predominant nickel species present in ambient air (urban background and rural) are soluble compounds constituting up to 95% of total nickel, with the remaining balance composed of insoluble nickel oxide complexes (Müller, 1999). In remote areas, annual mean nickel concentrations in air are around 1 ng/m^3 or less and in rural areas 0.5-2 ng/m^3. In urban areas, 2-20 ng/m^3 is a realistic exposure range. Heavily industrialized areas in most countries can be expected to have nickel concentrations from 10 to 100 ng/m^3 or higher.

Nickel emissions to the atmosphere may occur from natural sources such as windblown dust, volcanoes, and vegetation. In general, the main anthropogenic source of total nickel emissions into the ambient air is the combustion of oil and coal for heat or power generation. Lesser contributions can be derived from activities such as nickel mining and primary production, the incineration of waste and sewage sludge, steel manufacture, and electroplating (IPCS, 1991; Lewis and Caldwell, 1999). It should be noted that emissions from primary nickel production will not contribute to nickel in U.S. ambient air since there is no primary nickel production (mining, grinding, smelting and refining) in the United States. Some nickel is recovered in the form of a remelt alloy from by-products of certain nickel-using industrial operations and from spent batteries.

The kind of nickel species emitted depends strongly on the source type, though in almost all cases, emissions of metallic nickel from anthropogenic sources will be negligable. Different analyses of nickel in stack fly ash from oil-fired combustion units have shown that the predominant species are soluble nickel compounds with lesser amounts of oxidic nickel, and complex metal oxides containing nickel (spinels) (Bodog *et al.*, 1994; Zatka, 1992). Recently, X-ray absorption fine structure spectroscopy (XAFS) methodology was applied to identify the exact nickel species contained in power plant fly ash. The results indicate greater than 95% of the nickel in fly ash consists of hydrated nickel sulfate ($NiSO_4 \cdot xH_2O$) and Ni-bearing spinels such as trevorite ($NiFe_2O_4$) (Galbreath, 1999). Based on processes involved in metallurgical operations (stainless steel and nickel alloys production), it can reasonably be anticipated that the species emitted are predominantly insoluble oxidic nickel compounds and spinel forms, with trace amounts of metallic nickel and nickel-containing alloys.

Other minor sources of atmospheric emissions of nickel from high temperature processes include cement manufacturing and coke ovens. During cement manufacturing, nickel is emitted either as a component of the clays, limestones, and shales (raw materials) or as an oxide formed in high-temperature process kilns (IPCS, 1991). As the forgoing indicates, relatively little metallic nickel is emitted from industrial and commercial operations.

2.1.1.2 Occupational Exposures

Metallurgical operations (stainless steel and nickel alloys production and related powder metallurgy operations). There is no primary nickel production in the U.S. although some nickel is recovered in the form of a remelt alloy from by-products of certain nickel-using industrial operations and from spent batteries. Mean total nickel exposures of 0.045 mg Ni/m^3 were measured in 1993-1994 at a U.S. nickel alloy manufacturing plant by Vincent and coworkers (1995). Workers employed in these metallurgical operations were exposed primarily to oxidic nickel (85-90%), with a lesser contribution of metallic nickel and nickel alloys (~5%) as well as water-leachable forms of nickel (less than 10%) (Vincent *et al.,* 1995). Average exposures of 1.5 mg/m^3 metallic nickel were reported between 1956 and 1983 in a powder metallurgy operation in the U.S. (Arena *et al.,* 1998). Current exposures in powder metallurgy operations in Europe and North America tend to be lower. Average exposures of 0.1-0.5 mg Ni/m^3 (including metallic nickel and nickel oxides) have been reported, with concentrations ranging from 0.2-5 mg Ni/m^3 (Nickel Criteria Document, 1996)

Nickel-Cadmium batteries. Workers in nickel-cadmium battery manufacturing operations may have limited exposure to metallic nickel powders. Mean total nickel exposures in U.S. battery manufacturing plants of 0.04 (in 1988) and 0.075 mg Ni/m^3 (in 1981) have been reported (Hammel *et al.,* 1990; Boiano *et al.,* 1983). Metallic nickel is expected to constitute only a fraction of the total nickel exposures, with oxidic and soluble nickel exposures also present. There are very few nickel battery manufacturing operations (*e.g.,* Ni-Cd, Ni hydroxide, Ni metal hydride) in the U.S.

From the above, it is clear that while certain subgroups of workers in the U.S. may experience inhalation exposure to metallic nickel, for the most part their exposures will be well below the current OSHA PEL of 1.0 mg Ni/m^3.

2.1.2 Oral Exposure

Nickel in metallic form will not be present in drinking water or foods. Divalent nickel is the predominate form of nickel in aquatic sources. People in the U.S. will not experience exposure to metallic nickel through oral route.

2.1.3 Dermal Exposure

The general public may experience skin exposure through the use of nickel-plated articles such as inexpensive watches, jewelry, fasteners on clothing, *etc.* Occasional contact with massive forms of metallic nickel (anodes) could occur during nickel plating. Nickel-copper alloys are present in many U.S. coins, but pure metallic nickel or nickel-plated coins are not used in the U.S. Dermal exposure is possible wherever nickel powders are handled, such as in the powder metallurgy industry, and in the production of Ni-containing batteries, chemicals, and catalysts.

2.2 Toxicological Data

2.2.1 Human Data

In general, epidemiologic data from nickel workers have been difficult to interpret because of mixed exposures involving not only different nickel compounds but also other inorganic compounds (arsenic, cobalt, strong acid mists) and organic combustion products (ICNCM,

1990). However, with the continued acquisition of new epidemiologic data, a clearer picture is emerging with respect to the likely role that different nickel species play in human respiratory carcinogenesis. This picture is largely in agreement with what is currently known about these compounds from animal and *in vitro* studies and it indicates that metallic nickel does not present a human cancer risk via any relevant route of exposure.

Studies of past exposures and cancer mortality reveal that only respiratory tumors have been consistently associated with inhalation exposure to certain nickel compounds in nickel production operations. Data from ten different cohorts were presented in the report of the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990). These cohorts included approximately 80,000 workers involved in nickel operations (mostly mining, smelting, and refining, but some nickel alloy production and miscellaneous applications as well) located in the United States, Canada, England, Wales, Norway, Finland and New Caledonia. Of the examined workers, less than 10% had clear excess respiratory cancer risks. The excess risks were confined to workers in certain types of refining operations. No nickel-related excess respiratory cancer risks have been found in any nickel-using industry workers.

The ICNCM study analyzed data from refinery cohorts cross-classified by cumulative exposure and found no evidence of increased lung or nasal cancer risks associated with metallic nickel exposure. Within the nickel-using industry, the mortality of workers exposed to metallic nickel was studied by Enterline and Marsh, (1982), Cox *et al. (*1981) and Cragle *et al.* (1984). These three cohorts were also followed up in the ICNCM (1990) study. The lack of excess respiratory cancer risks in workers at the Oak Ridge gaseous diffusion barrier manufacturing plant was particularly notable as these workers were exposed solely to metallic nickel (Cragle *et al.*,1984). This is one of the few human studies available in which exposure to metallic nickel is not confounded by exposures to other nickel compounds. There was no evidence of increased respiratory cancer risks in this group of workers. Based on approximately 3,000 samples taken between 1948-1963, exposures were believed to be <1 mg Ni/m^3, with a median of 0.13 mg Ni/m^3 (90th percentile of 1.8 mg Ni/m^3). However, Cragle *et al.* (1984) stated that "under considerably improved working conditions, current levels of nickel reported [were] actually higher than historical data. Therefore, it is reasonable to assume that the reported median of 0.13 mg Ni/m^3 is biased toward the low side."

Likewise, in a recent update of a study on 715 hydrometallurgical workers in Canada, no excess lung or nasal cancers were reported (Egedahl *et al.,* 1993). Although the size of the cohort was small, exposures in this plant were solely to nickel concentrates and metallic nickel.

A study of U.S. high nickel alloy workers with metallic and oxidic nickel exposures is particularly important to note because of its size (>31,000 workers) (Arena *et al.*, 1998). Exposure data in the Arena *et al.* (1998) study were somewhat sparse, but in the powder metallurgy department (where exposures would likely have been solely to metallic nickel), average estimates of 1.5 mg Ni/m^3 of elemental nickel were reported. The workers in this department, albeit small in size, showed no nickel-related excess cancer risks. Average nickel exposures for the rest of the cohort (as either metallic, but more likely oxidic nickel) ranged from 0.01-0.3 mg Ni/m^3, with a median value of 0.08 mg Ni/m^3. These findings are further confirmed by a recent French study (Moulin *et al.,* 2000). In this study, a cohort of ~4,900 workers involved in the production of stainless and alloyed steel showed no significant increases in SMR for lung cancer mortality. A concurrent nested case-control study of lung cancer also failed to detect a relationship between this endpoint and exposure to metallic nickel and/or its compounds.

Examination of the available data shows that, even in the past, exposures to metallic nickel have generally been low (≤ 1 mg Ni/m^3) compared to exposures to various nickel compounds found in certain types of nickel refining operations. Therefore, the notable lack of epidemiologic evidence of increased cancer risk among workers exposed to metallic nickel could be due to the combination of relatively low-dose exposures and the limited bioavailability of the nickel ion from the metallic nickel particles found in the workplace. Whatever the case, under past and current industrial practices, it is clear that exposure to metallic nickel does not pose a respiratory carcinogenic risk for humans. This observation applies with even greater force in the case of general population exposures, which are far below occupational levels.

The forgoing discussion has focused on inhalation exposure to metallic nickel dust. There are no epidemiologic studies or clinical reports indicating an association between oral or dermal exposure to metallic nickel (*e.g.,* nickel-plated jewelry) and increased risk of cancer.

2.2.2 Mechanistic Data

Models for nickel-mediated induction of respiratory tumors suggest that the main determinant of the respiratory carcinogenicity of a nickel species is likely to be the bioavailability of the Ni (II) ion at nuclear sites of target epithelial cells (Costa, 1991; Oller *et al.*, 1997; Haber *et al.,* 2000). Only those nickel compounds that result in sufficient amounts of bioavailable nickel ions at nuclear sites of target cells (after inhalation) will be respiratory carcinogens.

The factors that will influence Ni (II) ion bioavailability in epithelial cells of the lung are: presence of particles on bronchio-alveolar surface, mechanism of lung clearance (dependent on solubility), mechanism of cellular uptake (dependent on particle size, particle surface area, particle charge), and intracellular release rates of Ni (II) ion. Those nickel compounds that are: (1) insoluble enough to allow accumulation of particles at cell surface, (2) have an intermediate lung clearance rate that allows them to persist in the lung, (3) have a high uptake of particles into epithelial cells via phagocytosis, and (4) undergo an increased release rate of Ni (II) ion inside the cells, will result in greater accumulation of Ni (II) ion at target sites. Inhalable size particles of nickel subsulfide represent a good example of a high Ni (II) bioavailability dust for respiratory carcinogenesis.

By contrast, soluble nickel compounds will not be present as particles on the cell surface (rather there will be Ni (II) ions and counter ions), will experience rapid clearance from the lung (decreasing the availability of Ni (II) ions for transport into the cell), will have inefficient transport through ion-transport membrane channels into target cells (*e.g.,* magnesium channels, Hausinger, 1992), and will avidly bind to proteins inside and out of the cells (Harnett *et al.,* 1982). The end result is that inhalation of soluble nickel compounds leads to very low bioavailability of Ni (II) ions at nuclear sites of target cells.

Based on the factors mentioned above, it can be predicted that very insoluble nickel species that are present as particles on the lung surface, have slow or intermediate particle clearance and efficient uptake into the epithelial cells via phagocytosis, but that have very low nickel ion release rates inside the cells also may fail to deliver high enough levels of nickel (II) ions at nuclear sites to elicit tumors. This may be the general model for elemental nickel dusts, since for metallic nickel, the release of Ni^{2+} ion is not based on solubility. Rather, deposited or phagocytized particles need to be oxidized to release Ni^{2+} ions.

Only inhalation studies can be used to evaluate the interaction of all the above mentioned factors that determine Ni (II) bioavailability. The NTP animal studies (NTP 1996 a,b,c) and the epidemiological data are consistent with the *nickel ion bioavailability theory* described above.

2.2.3 Animal data

Animal data often help to elucidate mechanisms of carcinogenesis or to provide perspective on epidemiologic results that are equivocal or confounded by other exposures. In the case of nickel compounds, the inhalation animal data for nickel subsulfide, green nickel oxide, and nickel sulfate hexahydrate (NTP, 1996 a,b,c) are in good agreement with the mechanistic data, and help us interpret the epidemiological results for soluble nickel. Unfortunately, a well-conducted inhalation animal bioassay for metallic nickel powder is lacking. A two-year inhalation cancer bioassay with elemental nickel powder in male Wistar rats is currently underway and will be completed in 2004. NiPERA is overseeing the conduct of this study. An OECD-compliant protocol is being used in the study, with supplemental lung burden analyses to assure absence of impaired lung clearance.

A number of limited animal inhalation studies with elemental nickel powder have not indicated carcinogenicity in rats or hamsters (Hueper, 1958; Hueper and Payne, 1962). Pott *et al.* (1987) intratracheally instilled nickel powder (unspecified particle size) containing 0.3 mg Ni and 0.9 mg Ni to groups of rats containing 39 and 32 animals, respectively, on a weekly basis (cumulative dose of 6 and 9 mg Ni, respectively). No clear dose-response was observed- 25.6% of the animals presented with either lung adenoma or carcinoma in the low–dose group and 25.0% in the high-dose group (0% tumors in saline control). Average survival of tumor-bearing animals was about 22-23 months. (Pott *et al.,* 1987). In another intratracheal instillation study in rats, increases in malignant tumors (although not in lung tumors) were observed at total cumulative doses of 20 and 40 mg Ni/animal of nickel powder (Ivankovic *et al.,* 1987). Significant toxicity was present in this study (survival time of 241 and 337 days compared to 500-544 days for controls), and no information on particle size of the powder was given. By contrast, intratracheal instillation of a cumulative dose of 10 mg nickel powder (12 times instillation of 0.8 mg Ni), of mass median diameter 3.1 µm, did not induce tumors in hamsters (Muhle *et al.,* 1992).

It should be noted that the relevance of intratracheal instillation as a route of administration for humans is highly questionable. Instillation produces heavier and more centralized particle deposition due to bolus delivery. In studies where the lung burden achieved by intratracheal instillation is massive, there is a potential for overloading lung clearance mechanisms and affecting the animal's ability to eliminate the material. These conditions can lead to false positive results. New guidelines for the conduct of intratracheal instillation studies have been recently recommended (Driscoll *et al.,* 2000). Injection studies of metallic powders, pellets or sponges by intraperitoneal, intramuscular, intraosseous, or intrarenal routes of exposure have given variable results (Hueper, 1955; Furst and Schlauder, 1971; Sunderman, 1984; Sunderman *et al.,* 1984; Jasmin and Riopelle, 1976; Pott *et al.,* 1987; Sunderman, 1989).

As discussed above, for respiratory cancer hazard identification, only inhalation studies should be considered, since only these studies can account for all the factors that can ultimately determine the respiratory carcinogenic potential of a given nickel-containing substance. There are no animal studies that have used the oral or dermal route of exposure to metallic nickel (massive or powder) to evaluate systemic or dermal carcinogenicity. The only animal studies showing evidence of tumorigenic response to metallic nickel powders involve non-relevant

routes of exposure, mostly in a single animal species (the rat), in animals experiencing high toxicity.

2.3 Carcinogenic Evaluations by Regulatory and Quasi-Regulatory Bodies

In 1990, IARC classified metallic nickel as a possible human carcinogen (Category 2B) based on animal injection studies. IARC considered the human data inadequate to characterize metallic nickel as carcinogenic. Since that time, additional studies of large cohorts of nickel alloy and stainless steel workers reported no significant increase in respiratory cancer risk (Egedahl *et al.,* 1993; Arena *et al.,* 1998; Moulin *et al.,* 2000). The most recent assessment of the potential carcinogenicity of metallic nickel was performed by the American Conference of Governmental Industrial Hygienists ("ACGIH"). In 1998, ACGIH adopted three different carcinogen designations for the various nickel species as part of its Threshold Limit Value ("TLV") program. Elemental/metallic nickel was placed in Category A5 - Not Suspected as a Human Carcinogen (ACGIH, 1999). In its most recent Update of the Toxicological Profile for Nickel, the Agency for Toxic Substances and Disease Registry ("ATSDR") also distinguished among different nickel species in the assessment of potential carcinogenicity. This reflected ATSDR's conclusion that, in assessing the potential health effects of nickel, "it is important to consider what form of nickel a person is exposed to and its bioavailability (ATSDR 1997, page 199). The Agency emphasized that "[n]o evidence was found that metallic nickel causes respiratory cancer" (ATSDR, 1997, page 54). U.S. EPA also has pointed out that, "inhalation studies have not shown that nickel in the metallic form will produce respiratory tract tumors." EPA went on to observe that even when the intramuscular injection studies are considered, the "tests are presently inadequate to support any definitive conclusions regarding [the] carcinogenicity [of metallic nickel] (EPA, 1986).

An IARC group has recently reviewed the carcinogenicity data on implants. Among their recommendations, the group indicated that implanted foreign bodies consisting of pure metallic nickel and metallic implants prepared as thin smooth films should be classified as Category 2B *(possibly carcinogenic to humans)* (McGregor *et al.,* 2000). However, it should be noted that people in the U.S. are not exposed to implants made out of pure metallic nickel.

2.4 Weight of Evidence Determination Regarding the Listing of Nickel Metal in the Tenth RoC

Under NTP's revised criteria, a substance may be listed as "*Known To Be a Human Carcinogen*" where "[t]here is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer." See NTP, 9th Report on Carcinogens, page I-2. There are several epidemiological studies of workers exposed to metallic nickel dusts. None of them has shown a causal association between cancer and exposure to metallic nickel. Clearly, nickel metal does not meet NTP's criterion for listing as a "*known human carcinogen.*"

Under NTP's revised criteria, a substance may be listed as "*Reasonably Anticipated To Be a Human Carcinogen*" when:

> "There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or

> there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset." See NTP, 9th Report on Carcinogens, page I-2.

The criteria go on to state:

> "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance." See NTP, 9th Report on Carcinogens, page I-2.

Application of these criteria under an overall weight-of-the-evidence approach leads to the conclusion that metallic nickel should not be classified as "*Reasonably Anticipated To Be a Human Carcinogen.*" As discussed above, epidemiological studies do not provide even limited evidence of a causal relationship between inhalation exposure to metallic nickel and increased risk of human cancer. Similarly, when route of exposure and mechanism of action are considered in reviewing the results of animal studies, the most appropriate weight-of-the-evidence conclusion—"based on scientific judgment"—is that metallic nickel cannot "*reasonably be anticipated to be a human carcinogen.*" The only animal studies showing evidence of tumorigenic response involve non-relevant routes of exposure, mostly in a single animal species (the rat), in animals experiencing high toxicity. By contrast, there is no evidence for the carcinogenicity of metallic nickel via inhalation, ingestion, or dermal exposure in epidemiological or animal studies. Moreover, from a mechanistic perspective, nickel metal—which must be oxidized to release Ni (II) ions inside lung epithelial cells—has a relatively low nickel ion release rate and thus is unlikely to be an effective respiratory cancer initiator.

In these circumstances, metallic nickel cannot "reasonably be anticipated to be a human carcinogen" by any relevant route of exposure. Metallic nickel should, therefore, be removed from the list of substances that are "*reasonably anticipated to be a human carcinogen*" when NTP publishes the 10th RoC.

– PART 2 –

3. NICKEL-CONTAINING ALLOYS

3.1 NATURE AND PROPERTIES OF NICKEL-CONTAINING ALLOYS

An alloy is a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. Alloys contain two or more metals and often non-metallic elements such as carbon and nitrogen as well. The manufacturing processes are carefully controlled to produce alloys with distinct properties, different from those of the metals from which they were made, making them unique for the purposes for which they are intended. During manufacture of most alloys, the constituents are heated to very high temperatures, usually above their melting points. They react and dissolve into each other to form alloys consisting of new crystalline structures (oxidic compounds are also produced in the process). As a result, 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 carcinogenicity of nickel alloys must, therefore, be evaluated separately from the potential carcinogenicity of nickel metal itself, since the potential carcinogenic hazard of a nickel-containing alloy cannot be simply related to the concentration of nickel or any other metal in that alloy.

There are hundreds of different nickel-containing alloys in many different product categories - the so called "superalloy" nickel alloys, stainless steels, alloy steels, cast-irons, etc. The majority of nickel used, however, would occur in the first two categories - stainless steel and nickel alloys. High nickel alloys are mostly Ni-Cu, Ni-Fe, Ni-Cr, and Ni-Fe-Cr. Representative compositions of the various families of stainless steel and nickel alloys are given below..

Composition of Selected Stainless Steels and Nickel Alloys (ASM Specialty Handbook: Stainless Steels, 1994)

Unified Numbering System (UNS) designation	Common Name	Maximum percent weight of main components				
		Mn	Cr	Ni	Mo	Other
Ferritic Stainless S43000	430	1.0	16.0-18.0			0.12 C, 1.0 Si, 0.03 S, 0.04 P
Martensitic Stainless S4100	410	1.0	11.5-13.0			0.15 C, 0.5 Si, 0.03 S, 0.04 P
Austenitic Stainless S30400	304	2.0	18.0-20.0	8.0-10.5		0.08 C, 1.0 Si, 0.03 S, 0.045 P
Duplex Stainless S31803	2205	2.0	21.0-23.0	4.5-6.5	2.5-3.5	0.03 C, 1.0 Si, 0.02 S, 0.08-0.2 N, 0.03 P
Precipitation Hardening Stainless S17400	17-4PH	1.00	15.5-17.5	3.0-5.0		0.07 C, 1.0 Si, 0.03 S, 0.2-0.5 Nb, 3.0-5.0 Cu, 0.04 P
Nickel-Base Alloy N06625	625	0.05	22.0-23.0	58.0	8.0-10.0	0.01 C, 0.5 Si, 0.02 S, 3.2-4.2 (Cb-Ta), ≤ 5.0 Fe, 0.015 P

Alloys are specifically formulated to meet the need for manufactured products to possess certain physical, mechanical and corrosion-resisting properties. These include magnetic, thermal expansion, strength, and heat-resisting properties, and corrosion resistance in various

media. 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 air, water and aqueous solutions 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.

The examples provided below demonstrate differences among the properties of various nickel containing alloys and elemental nickel. Metals will become bioavailable, and hence potentially able to exhibit biological effects, only following their release into a medium *via* corrosion.

Example 1. The European Directive 94/27/EC is designed to protect people against the development of dermal sensitization to nickel as a result of close and prolonged contact of the skin with nickel-containing articles (*e.g.*, jewelry). The Directive requires, *inter alia*, that articles should be tested according to EN 1811-1998 to determine the amount of nickel released into "artificial sweat" (EC, 1999b). Only metals and alloys that release less than 0.5 micrograms of nickel per square centimeter per week are allowed to be used in jewelry. The following test results show the maximum values recorded and the differences for several materials (Carter, 1999).

Alloy/metal	Nickel content	Ni release (µg/cm²/week)
"Nickel silver" (Cu,Ni,Zn)	10%	18.4
Stainless steel, grade 304	8-10.5%	<0.02
Commercially pure nickel	>99%	1.44

In this case, the commercially pure nickel failed the test, but the stainless steel had extremely low nickel release, much less than predicted based on percent of nickel (<0.02 versus 0.14 predicted). It should be noted, that the "nickel silver", with a similar nickel content to the stainless steel, had a high level of release into the artificial sweat, more than predicted based on percent of nickel (18.4 versus 0.14 predicted).

Example 2. A series of tests in a rig designed to simulate a domestic water system demonstrates the large differences in reaction and transfer of reaction products from metals and alloys into the water (CRECEP, 2000). The values below are the highest observed from all the test conditions.

Test material	Composition	Metal release (µg/liter)
Stainless steel	18-20% Cr; 8-10.5% Ni; ~70%Fe	Cr: <10; Ni: <10; Fe: 60
Gunmetal	Cu Sn Zn Pb Ni (0.9%Ni)	Ni: 250

It should be noted that nickel release from the stainless steel containing up to 10.5% nickel was below the limit of detection, while the gunmetal, containing less than 1% nickel, released 25-times the detectable amount.

It should be recognized then that nickel-containing alloys have their own specific properties distinct from those of elemental nickel. Carcinogenic hazard determination for a nickel-containing alloy should, therefore, be based on the physical, chemical, metallurgical and toxicological properties of the alloy itself, not on the properties of its constituent elements, including elemental nickel.

3.2 ROUTE OF EXPOSURE

3.2.1 Inhalation Exposure

3.2.1.1 Ambient air

The most common forms of nickel in ambient air are nickel sulfate, complex nickel oxides, and complex nickel-ferric oxides. There are no significant amounts of metallic nickel or nickel-containing alloys in ambient air (Müller, 1999). The main potential sources of nickel alloy emissions into the ambient air are metallurgical operations such stainless steel production and high nickel alloy manufacturing (both massive and powder forms) operations. Even in those cases, based on the processes involved, it can reasonably be anticipated that the species emitted are mostly insoluble oxidic nickel and spinel forms, with trace amounts of metallic nickel and nickel-containing alloys. Other minor sources of atmospheric emissions of nickel alloys include catalyst production.

3.2.1.2 Occupational Exposure

Metallurgical operations (stainless steel and nickel alloy production). Workers employed in these metallurgical operations will be exposed primarily to oxidic nickel, with a lesser contribution of combined metallic nickel and nickel alloys (~5%), as well as water-leachable forms of nickel (Vincent *et al.,* 1995).

Production of stainless steel powders. There is only one company in the United States that produces stainless steel and other nickel alloy powders. While statistics are not available, it is reasonable to believe that such nickel alloy powders amount to less than 0.1% of total U.S. stainless steel and nickel alloy production. Inhalation exposure to stainless steel powders may occur during their manufacture and use (*e.g.,* plasma spraying operations).

Processing of stainless steel. Processing of stainless steel includes welding, grinding, cutting, polishing and forming. A number of different methods are used for welding. Welding fumes are complex mixtures of particles and gases. Welding fume particles are mainly of respirable size. The composition of the fume will depend largely on the welding process employed and the welding consumable used. The consumable electrode, not the base metal, is the major source of fume. The nickel content of fume from welding of stainless steel has been reported to exist predominantly in complex iron oxides and potassium chromates (not alloys) and represent 0.2-4.9% of the total fume (AWS, 1983). Fumes from nickel and nickel-base alloy welding electrodes typically contain about 10% nickel in the form of oxides and potassium chromates. Therefore, welding is not a source of alloy exposure *per se* and should be considered on its own as a potentially carcinogenic process.

Grinding of stainless steel and high nickel alloys generates dust of variable particle size. Larger particles (> 8 µm) have the composition of the alloys, while finer material (respirable size) is made up of spinels (Lausch, 1999). Spinels are different from stainless steel and include complex metal oxides (*e.g.,* nickel-chrome-iron spinels and nickel-iron spinels). It should be noted that operations such as grinding and welding are usually carried out in enclosed environments or by workers using protective equipment.

3.2.2 Oral Exposure

Powders of nickel-containing alloys will not be present in drinking water. Ingestion of metal ions released from stainless steel cooking pots may represent a potential route of exposure to soluble nickel for the general public, but it does not represent a source of intake of the alloy itself. Studies of the release of Cr and Ni from stainless steel (AISI 304 and 436) cooking utensils into food have provided evidence that some nickel and chromium ions are released but that their relative contributions to the diet are small since nickel is a natural constituent of many foods (Kumar *et al.,* 1994; Accominotti *et al.,* 1998; Flint and Packirisamy 1997).

3.2.3 Dermal Exposure

The population of the United States will experience dermal exposure to massive forms of nickel-containing alloys every day through contact with flatware, doors and door hardware, railings, pots and pans, tools, machinery, needles, pins, fasteners, jewelry, watches, cabinets: wherever the common forms of stainless steel are present. 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 release rates were close to or exceeded the 0.5 $\mu g/cm^2$/per week limit specified in the Nickel Directive of the European Union (Directive 94/27/EEC) is Type 303 (a specialty 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 0.03 $\mu g/cm^2$/per week (Haudrechy *et al.,* 1994; Haudrechy and Pedarre, 1997). Stainless steels that release less than 0.5 $\mu g/cm^2$/per week will not provoke an allergic skin response in the majority of nickel-sensitized subjects even when in prolonged and intimate contact with the skin (Menne *et al.,* 1987).

The general public also has intermittent dermal contact with nickel-copper alloys in coinage. United States coinage (with the exception of the penny) contains nickel in different alloy forms. Those workers who handle large volumes of coinage - such as cashiers- can be considered to be occupationally exposed to nickel alloys. It should be noted that besides a few case-reports of dermatitis, no other adverse health effects have been associated with these exposures.

Dermal exposure to nickel alloy powders may occur in the powder metallurgy industry that produces and uses stainless steel and nickel alloy powders, and in catalyst production.

3.3.4. Prosthetic Implants and Dental Appliances

Metals have been used as biomaterials for many years. The composition of some of the nickel-containing alloys used as surgical implants is shown below (Donachie, 1998).

Composition of Main Nickel-Containing Alloys Used as Surgical Implants

Alloy	Composition %					
	C	Cr	Fe	Co	Ni	Mo
AISI type 316 stainless steel	≤0.08	18.5	Balance		12.0	3.0
AISI type 316L stainless steel	≤0.03	16-18	Balance		10-14	2-3
Cast cobalt-chromium alloy	≤0.36	28.5	≤0.75	balance	≤2.5	6.9
Wrought cobalt chromium alloy	≤0.15	20.0	≤3.0	balance	≤2.5	
Co-Ni-Cr—Mo (MP35N)		20.0		35.0	35.0	10.0

Three main groups of alloys are used for surgical and medical instruments and body implants: stainless steels, Co-based alloys, and Ti-based alloys (no nickel). For structural applications in the body, the principal alloys used are 316L stainless steel, cobalt-chromium alloys, and Ti-6Al-4V (no nickel) alloy. Alloys in articulating prosthesis applications are often used in conjunction with other biomaterials such as polymers (*e.g.,* polyoxymethylene) or ceramics (*e.g.,* aluminum oxide). Austenitic stainless steel alloys are popular because their mechanical properties can be controlled over a wide range for optimum strength and ductility. Minimal corrosion of stainless steel is enhanced by nitric acid passivation. Nonetheless, stainless steels are not used as long-term implant material. Early hips implanted in the 1960s used stainless steel, but cobalt-chromium or titanium alloys are now the metallic materials of choice for long-term implants. Stainless steels are still used in bone screws, bone plates, intramedullary rods and other temporary fixation devices. Types 302, 304, 304VAR and 316L stainless steel have been used as wire for limited duration applications in the body. Nickel-titanium alloys of approximately equiatomic composition are shape memory effect alloys that are used in osteosynthesis plates, jaw plates, and dental braces. These alloys are corrosion resistant and can be used for temporary fracture fixation. To improve bone attachment, metal implants are often coated with calcium phosphate. For dental implants, cast chromium-cobalt alloys and nickel-chromium alloys (including austenitic stainless steel) are used for fixed bridges and partial dentures and are available as wires for orthodontic use. These materials allow the manufacturing of lighter and thinner dental prostheses (Donachie, 1998). Exposure in patients with metal on metal implants (older types) could be to corrosion products that may include solubilized metal ions (*e.g.,* Cr, Ni, Fe, Mo) and wear particles or metal precipitates, depending on the composition of the implant (Hildebrand *et al.,* 1988). A diminished metal ion release from currently used implants appears to be due to the use of more corrosion resistant alloys and by minimizing mechanical failure and abrasion (Török *et al.,* 1995).

3.3 Toxicological Data

3.3.1. Human Data

3.3.1.1 Inhalation

There are no epidemiologic studies where exposures are only to powders of nickel-containing alloys. In studies of cohorts of high nickel alloy workers there has been no evidence of increased lung and nasal cancer risks associated with workplace exposures (Enterline and Marsh,1982., Cox *et al.* 1981; ICNCM, 1990; Arena *et al.*, 1998). In the stainless steel and alloy manufacturing industry, exposure to nickel alloys is a minor component of the exposure to total nickel-containing substances.

Cornell (1984) studied the proportional cancer mortality ratio based on ~4,500 U.S. workers employed in the manufacturing of stainless steel and low nickel content alloys. No exposure data were provided in the study, and no evidence of occupationally related lung cancers was found. In a more recent study of U.S. high nickel alloy workers (>31,000 workers) an overall significant 13% increased risk of lung cancer was noted when mortality rates were compared to the total U.S. population (Arena *et al.*, 1998). However, no significant excess was identified when local populations were used for comparison, and even the slight excess risk found in the comparison to the U.S. population (13% increased risk) could be explained by a confounding factor such as smoking.

Moulin and collaborators (Moulin *et al.,* 1990; Moulin *et al.,* 1993a) have looked at the cancer mortality experienced by French workers producing ferrochromium and stainless steel (~2,300

workers, Moulin *et al.*, 1990) and just stainless steel (4,200 workers, Moulin *et al.*, 1993a). Excess lung cancer mortality was found in the former cohort, in association with employment in the ferrochromium but not the stainless steel plant. In the second cohort, no elevated lung cancer risk was apparent for workers involved in (non-foundry) stainless steel production operations (melting shop). These findings are further confirmed in a recent study update (Moulin *et al.*, 2000). In this study, a cohort of ~4,900 workers involved in the production of stainless and alloyed steel showed no significant increases in SMR for mortality of lung cancer. A concurrent nested case-control study of lung cancer also failed to detect a relationship between this endpoint and exposure to nickel and/or its compounds.

As mentioned in section 3.2, during the processing of stainless steel in such operations as grinding and welding, workers are mostly exposed to complex nickel oxides (spinels) with less significant exposures to nickel alloy dusts and/or fumes. Studies of Swedish workers involved in the grinding of stainless steel include the study of workers manufacturing stainless steel (18% nickel) sinks and pans (Svensson *et al.*, 1989, Jakobsson *et al.*, 1997). These workers were engaged in activities such as grinding, finishing, and polishing. The findings from this study do not indicate that occupationally-related lung cancers have occurred in this cohort. A Danish study of stainless steel welders and stainless steel grinders showed non-significant increases for overall cancer incidence and cancers of the respiratory system in a subgroup of ~500 grinders. (Hansen *et al.*, 1996). Together, the studies of cancer risks in grinders of stainless steel do not indicate that such work leads to excess risk of respiratory cancer.

In the Arena *et al.* (1998) study of high nickel alloy workers, although no excess respiratory cancer mortality was found, a significant excess risk for colon cancer in non-white male workers was observed using both U.S. or local comparison populations as reference. Work-specific findings suggested the elevated mortality risk from colon cancer was confined to non-white males in grinding, allocated services, and the miscellaneous category. The authors noted that the number of non-white workers was small, and it was not clear to what extent the elevated colon cancer risk was plant-specific. Moreover, there was no indication of excess mortality from colon cancer among white males or females. An increase in work-specific kidney cancer risk among white males employed in "melting" (mostly oxidic nickel exposures) also was observed. However, the number of deaths attributed to kidney cancer was small, so it was difficult to assess the nature of this finding. Moreover, analysis by duration of employment and length of time since first employment revealed no significant excess in mortality among high nickel alloy workers for lung cancer, kidney cancer, colon cancer, or ischemic heart disease. In addition, it is worth noting that, in the ICNCM study (1990) of ten different cohorts, "no substantial evidence was obtained to suggest that occupational exposure to nickel or any of its compounds was likely to produce cancers elsewhere than in the lung or nose."

As mentioned in section 3.2, the nickel content of fume from welding of stainless steel has been reported to exist predominantly as nickel oxides (not nickel alloys) and represents 0.2-4.9% of the total fume. Therefore, welding is not a source of alloy exposure *per se* and may not be relevant for evaluating the possible carcinogenicity of nickel-containing alloys. Given the fact that welding involves, to a minor extent, exposures to other types of nickel compounds, a brief consideration of the most recent epidemiologic studies of nickel welders is presented. It should be noted that welders will have exposures to other metal compounds besides nickel (notably chromium) and to contaminants such as oil and grease present on the surface of the material being welded. In 1990, IARC considered "welding" a process that required its own separate listing (*possibly carcinogenic to humans, group 2B*).

Since IARC's pronouncement, Becker *et al.* (1991) and Simonato *et al.* (1991) have found no evidence of excess lung cancers specifically associated with welding. Excess lung cancer mortality was not associated with duration of employment or cumulative exposure to total fume, total chromium, or nickel (Simonato *et al.*, 1991). This was one of the largest cohorts studied to date, consisting of ~11,000 welders of stainless steel, mild steel, and shipyard welders. Further analyses of this cohort (Gerin *et al.*, 1993) showed no trend for lung cancer risk for three categories of nickel exposure. A study of ~2,700 French welders did not indicate increased risk of lung cancer in stainless steel welders (Moulin *et al.*, 1993b). No excess in cancer incidence among Norwegian welders of mixed stainless steel/mild steel was found by Danielsen *et al.* (1996). A Danish study of stainless steel welders and stainless steel grinders provides evidence of increased risk of lung cancer in welders but fails to demonstrate a causal association for stainless steel (nickel-containing alloys) or mild steel (non-nickel alloy) welding (Hansen *et al.*, 1996).

Milatou-Smith (1997) found a non-significant excess of lung cancer among stainless steel welders, although the cohort was small (233 men). A meta analysis of 36 epidemiologic studies in welders was recently conducted by Moulin (1997). This analysis demonstrated an elevated relative risk of lung cancer in the unspecified welding category, but no evidence of increased risk specifically associated with stainless steel welding. The authors concluded that the elevated lung cancer in welders *"cannot be explained by hexavalent chromium and nickel exposures among stainless steel welders."* A more recent paper by Becker (1999) suggests that increased respiratory cancer risk in welders can be accounted for by exposure to asbestos. No indication of elevated risk specifically associated with exposure to welding fumes containing chromium and nickel could be determined in this study. For a recent comprehensive review of the health effects associated with the manufacture, processing, and use of stainless steel see Cross *et al.*, (1999).

No human data are available for workers mainly involved in cutting, polishing or forming of stainless steel. As described above, the available epidemiologic data for workers involved in other stainless steel processing activities do not demonstrate a causal association between nickel alloy exposure and excess cancer risk.

3.3.1.2 Implants

The most recent statistics on implants suggest that as many as 6.5 million metallic orthopedic implants were in use in the U.S. population in 1988, including 1.6 million artificial joints and 4.9 million fixation devices (Sharkness *et al.*, 1993). Given the aging demographics of the U.S. population, many more implants are likely in use today. Despite the millions of implants that have been used in the past 30 to 40 years, only 35 cases of tumors involving bone or soft tissue in the region of the implants have been reported (McGregor *et al.*, 2000). In addition, of fourteen cohort studies which have been performed to investigate cancer incidence in patients following total knee or hip replacements, only one study has shown an increase in overall cancer incidence, and this incidence was noted to be small (Nyren *et al.*, 1995; McGregor *et al.*, 2000).

While overall cancer incidences have not generally been shown to be elevated in association with the use of metal prostheses, a few studies have suggested an excess risk at specific sites, mainly lympho-hematopoietic. Examination of some of these studies reveals a lack of statistical significance (Coleman, 1996) or relationship with follow-up time (Paavolainen *et al.*, 1999). In a small cohort study of 1,358 patients in New Zealand, the occurrence of lymphatic and hematopoietic cancer was increased after two years of follow up in patients with hip prostheses

which had been implanted from 1966 to 1973 (Gillespie *et al.,* 1988). However, in a later review article of more recent studies, Gillespie *et al.* (1996) failed to observe lympho-hematopoietic cancers in two matched cohort studies and a case control study undertaken in North America and Scotland. The authors speculated that the lympho-hematopoietic cancers seen in the New Zealand study may have been due to the usage of metal on metal prostheses which were more commonly used in the 1960s-1970s than they are today. No specific information on the alloy composition of the implants was included in this paper. Lack of evidence for increased lympho-hematopoietic cancers also has been noted in a much larger cohort study (39,000 patients) conducted in Sweden (Nyren *et al.,* 1995). Moreover, the authors of a recent IARC position paper evaluating the carcinogenic risks to humans associated with surgical implants and other foreign bodies noted that, in the few studies where lympho-hematopoietic cancers have been observed, these studies failed to provide information on possible confounding variables, such as immunosuppressive therapy or rheumatoid arthritis (McGregor *et al.,* 2000).

NiPERA believes that for "implants," as for "welding," a separate carcinogenic assessment and listing should be considered. This would be consistent with the fact that surgical implants are regulated as medical devices by the Food and Drug Administration under 21 C.F.R. Part 888. Based upon the evidence from both human and animal data, IARC concluded that orthopedic implants of complex composition (most implants on the market today, including surgical stainless steel) were not classifiable as to their carcinogenic potential to humans, *i.e.,* they were classified as Group 3 carcinogens (McGregor *et al.,* 2000).

There are no studies or clinical reports that indicate an increased carcinogenic risk from use of dental devices made with nickel-containing alloys (Moffa, 1982).

3.3.1.3 Dermal Exposure

There have been no epidemiologic or clinical reports of an association between dermal exposure to massive forms of nickel-containing alloys and increased risk of cancer.

3.3.2 Mechanistic Data

Alloys of different metal composition have different properties that are unique to that type of alloy. With regard to biological properties, it is not possible to predict the toxicity of an alloy just based on the properties of its metal constituents. The combination of metals (and their proportions) in an alloy can modulate the release rate and bioavailability of a particular metal ion. Alloys with higher corrosion resistance are expected to present lower biological hazard.

The main determinant of the respiratory carcinogenicity of a nickel-containing substance is likely to be the bioavailability of the Ni (II) ion at nuclear sites of target epithelial cells (Costa, 1991; Oller *et al.*, 1997; Haber *et al.,* 2000). Only those nickel-containing substances that result in sufficient amounts of bioavailable nickel ions at nuclear sites of target cells (after inhalation) will be respiratory carcinogens.

As mentioned in section 2.2.2, the factors that will influence Ni (II) ion bioavailability in epithelial cells of the lung are: (1) presence of particles on bronchio-alveolar surface, (2) mechanism of lung clearance (dependent on solubility), (3) mechanism of cellular uptake (dependent on particle size, particle surface area, particle charge), and (4) intracellular release rates of Ni(II) ion. Very insoluble nickel species that are present as particles on the lung surface, have slow or intermediate particle clearance and efficient uptake into the epithelial cells via phagocytosis, but have very low nickel ion release rates inside the cells may fail to deliver high enough levels of

nickel (II) ions at nuclear sites to elicit tumors. This may be the case for most of the nickel-containing alloy powders and, as mentioned in the previous section, for metallic nickel dusts. It should be noted that for metallic nickel (Ni^0), the release of Ni^{2+} ion is not based on solubility. Rather, deposited or phagocytized particles need to be oxidized to release Ni^{2+} ions. For nickel-containing alloys, the proportion of nickel in the alloys does not, by itself, predict the extent of nickel bioavailability. The presence of other metals in these alloys may increase or decrease the rates of oxidation and release of Ni^{2+} ions compared to the release rates from elemental nickel.

For respiratory carcinogenicity, only inhalation studies can be used to evaluate the interaction of all the above mentioned factors that determine Ni (II) bioavailability. For other routes of exposure (*e.g.,* implants), the corrosion rates of massive forms of the alloys will need to be evaluated under relevant conditions.

3.3.3 Animal data

As mentioned in section 3.2, human exposures to nickel-containing alloy dusts are very limited. Very sparse animal data are available to evaluate the respiratory carcinogenicity of nickel alloys. A well-conducted animal bioassay by inhalation for nickel-containing alloy dusts is lacking. A two-year inhalation cancer bioassay with elemental nickel powder in male Wistar rats that is currently underway may be somewhat relevant for nickel-containing alloy dusts (2004 completion date).

One intratracheal instillation study looked at two types of stainless steel grinding dust. An austenitic stainless steel (18/10 Cr-Ni, 6.8% nickel, aerodynamic diameter less than 6 µm) and a chromium ferritic steel (0.5% nickel, aerodynamic diameter less than 4.5 µm) were negative in hamsters after repeated instillations for a total cumulative dose of 108 mg/animal (Muhle *et al.,* 1992). In another study, grinding dust from an austenitic stainless steel (26.8% nickel) was generated by applying a water jet to molten alloy, followed by grinding (Ivankovic *et al.,* 1988). In this study, hamsters received a single or repeated instillations for a total cumulative dose of up to 80 mg dust/animal. No evidence of carcinogenicity was observed. In the same study, an alloy containing 66.5% nickel, 12.8% chromium, and 6.5% iron was tested. At doses of 20 mg and above (cumulative dose), an increased incidence of malignant tumors was observed with evidence of a dose-response. It should be noted that none of the tumors were lung tumors and that survival was significantly reduced in the treated animals indicating a significant level of toxicity.

Intraperitoneal rat injection studies with ground alloy powders (particle diameter less than 10 µm) of different composition were carried out by Pott *et al.* (1992). Single or double injection of 50 mg Ni/animal (cumulative dose of 50 to 100 mg Ni/animal) of a nickel alloy powder containing 29% Ni and 21%Cr, failed to significantly increase the incidence of tumors in Wistar rats. A sample of a nickel alloy containing 66% nickel and 16% chromium, at 50 and 150 mg Ni/animal gave a significant increase in the number of combined mesotheliomas and sarcomas. Similar positive results were found with a nickel-aluminum alloy containing 50% nickel, 50% Al (Pott *et al.,* 1992).

Data on the effects of implants in animals comes from both experimental and veterinary studies of massive and/or powder (less relevant) forms of the materials used in the manufacturing of implants. Implantation can be in soft tissues, intramuscular, or intramedullary. In a review of studies regarding the implantation of alloys in experimental animals (mainly rats), Sunderman (1989) reported mixed results. No implantation-site tumors were seen in rats administered

various nickel-containing alloys as rods (Gaechter *et al.,* 1977) or as a NiCoCrMo powder (Pauli *et al.,* 1986). On the other hand, sarcomas and lymphomas were seen in rats administered NiGa pellets (Mitchell *et al.,* 1960). The carcinogenic potential of twenty-two solid, fiber, or powder metal alloys and ceramic materials was studied by intramedullary implantation in bones of rats (Memoli *et al.,* 1986). Implantation-site sarcomas were observed in 1/26 animals implanted with a Co-based alloy powder, 3/26 animals that received a CoCrWNi fiber porous composite (prepared as 50% dense pellets), and 3/26 animals implanted with NiCoCrMo alloy (MP35N) powder. By contrast, animals implanted with rods of stainless steel 316L, pure titanium, Ti6A14V alloy, CoCrMo alloy, NiCoCrMo alloy (MP35N), and CoCrWNi alloys did not exhibit these tumors. For all treatment conditions, the incidence of lymphomas was similar to the spontaneous incidence in concurrent and historical controls. The influence of inflammation on the observed tumor responses was not examined. The authors noted that the intramedullary location of the implanted material used in this study could have played a role in the observed increased incidence of malignant tumors.

Smooth surface cylindrical rods of various alloys, including stainless steel 316L (containing 12.5% nickel) and a high nickel content alloy (96% nickel) were implanted in the thigh muscle of mice (Takamura *et al.,* 1994). Tumor development at the implantation site was examined after 24 months. No implantation site sarcomas occurred in the stainless steel (AISI 316L) treated animals. Three of the 50 animals exposed to stainless steel rods had lymphomas near the implantation site. These lymphomas have been postulated to be related to the local inflammatory response. By contrast, tumors at implantation site were found in 21/23 mice implanted with rods of high nickel content alloy, although these animals experienced very high mortality.

During the conduct of a carcinogenicity study with cadmium chloride in Wistar rats, one group of animals with NiCu ear tags (65% Ni, 32% Cu, 1.3% Fe, 0.8% Mn, 0.2% Cr) exhibited 8% incidence of tumors at the site of the tags. A second group of animals wearing tags of similar metal composition showed a 1% incidence of tumors at the insertion site (Waalkes *et al.,* 1987). The authors postulated that the presence of chronic inflammatory reactions in the first, but not the second, group of animals could be related to the differences in the observed tumor response.

In veterinary studies of dogs, Sunderman (1989) describes twelve case-reports of sarcomas that developed adjacent to metallic implants (stainless steel and unspecified alloys). Besides the implants themselves, the author noted that the presence of trauma, delayed healing of fractures, and osteomyelitis could have been contributing factors to the observed tumors. In a case-control study, Li *et al.* (1997) found no association between metallic implants used to stabilize fractures in dogs and the development of soft tissue tumors. The conclusion reached by IARC regarding veterinary studies is that the evidence for the carcinogenicity of metallic implants and metallic foreign body implants is inadequate to make any determinations regarding the carcinogenicity of such implants in dogs (McGregor *et al.,* 2000).

The tumor response to foreign bodies still remains poorly understood. Persistent tissue irritation and inflammation by the foreign body can lead to tumor formation at the implantation site (Sharkness *et al.,* 1993). Tumor induction is partially dependent on the chemical composition of the material, and more closely dependent on its physical properties (*e.g.,* smooth surfaces promote tumor induction better than rough surfaces). This phenomenon has been observed and described in rodent models but its significance for humans remains unknown. As noted by IARC, most nickel-based alloys that have been tested for carcinogenicity in animals are not

actually used in clinical devices or have been tested in a powder, rather than massive form (McGregor *et al.*, 2000).

In summary, the preponderance of information on clinically-relevant alloys suggests that exposure of animals to such alloys via prosthetic devices does not constitute a significant health hazard. IARC concluded that the carcinogenic evidence for stainless steel prostheses in animals was inadequate to make any determinations regarding carcinogenic classifications.

3.4 Carcinogenic Evaluations by Regulatory and Quasi-Regulatory Bodies

Both the EU and the OECD have characterized alloys as mixtures or "preparations" whose toxicological properties may be similar to or different from those of their metal constituents depending only on the concentration of the metals in the alloy. In the most current European Union Directive 1999/45/EC (EC, 1999a, recital 10), it is noted that "whereas the characteristics of alloys are such that it may not be possible to determine their properties using currently available conventional methods...it is therefore necessary to develop a specific method of classification which takes into account their particular chemical properties." Due to the unique properties of alloys, the European Commission has contracted a separate working group to design a new hazard classification system for alloys. Similarly, in the Step 2 Proposal for Harmonized Classification Criteria for Mixtures (OECD, 2000, paragraph 12), OECD now acknowledges that special problems exist in using the current scheme for metallic alloys, and that "consideration of the classification of metallic alloys has been set aside and guidance will be developed at a later date."

With regard to implants, an IARC group has recently recommended that orthopedic implants of complex composition (including stainless steel, Co-based, and Ti-based alloys) be classified as Category 3 (*not classifiable as to their carcinogenicity to humans*) (McGregor *et al.*, 2000). As far as we are aware, these are the only types of nickel-containing implants currently used in the United States. By contrast, implanted foreign bodies consisting of metallic nickel and one specific alloy powder (66-67% nickel, 13-16% chromium, and 7% iron), as well as metallic implants prepared as thin smooth films are recommended for classification as Category 2B *(possibly carcinogenic to humans)*. Persons residing in the U.S. do not receive implants made out of metallic nickel or powders of alloys.

3.5 Weight of Evidence Determination Regarding the Listing of Nickel Alloys in the Tenth RoC

Under NTP's revised criteria, a substance may be listed as "*Known To Be a Human Carcinogen*" where "[t]here is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer." See NTP, 9th Report on Carcinogens, page I-2. There are several epidemiologic studies that included workers exposed to dusts containing nickel alloys. None of the studies have shown a causal association between cancer and inhalation exposure to dusts in the workplace.

Under NTP's revised criteria, a substance may be listed as "*Reasonably Anticipated To Be a Human Carcinogen*" when:

> "There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative

explanations, such as chance, bias or confounding, could not adequately be excluded, or

there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset." See NTP, 9th Report on Carcinogens, page I-2.

Applying these criteria to the overall weight of the evidence for nickel alloys it is clear that nickel-containing alloys should not be listed in the Tenth Report on Carcinogens at all because: (1) there is no evidence from human studies of increased cancer risk causally associated with nickel alloy exposures, and (2) the only animal studies showing evidence of a tumorigenic response involved non-relevant routes of exposure with nickel alloy powders, or implantation of high nickel alloys not currently used in human implants. By contrast, there is no evidence of carcinogenicity for nickel alloys via inhalation, ingestion, or dermal exposure in humans or animals. Accordingly, there is no basis for "reasonably anticipating" that nickel-containing alloys are carcinogenic to humans via a route that is relevant to the potential exposures of persons residing in the United States. Therefore, NTP should not list nickel alloys in the Tenth RoC[1].

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[1] As noted above, NiPERA believes that NTP might wish to evaluate implants of various types as a separate nomination for possible listing in a future edition of the Report on Carcinogens.

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