NiPERA INC.
Nickel Producers Environmental Research Association

November 29, 2000

RECEIVED
NOV 30 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:

Enclosed you will find comments of the Nickel Producers Environmental Research Association (NiPERA) on NTP's proposal to list **Metallic Nickel and Certain Nickel Alloys** *as reasonably anticipated to be human carcinogens* in the 10th Report on Carcinogens. In addition, detailed comments on the draft RoC Background Document for **Metallic Nickel and Certain Nickel Alloys** can be found in Attachment 1.

As indicated in the NiPERA comments, the available evidence does not indicate that metallic nickel or nickel-containing alloys can reasonably be anticipated to be carcinogenic to humans by routes of exposure that are relevant to people residing in the U.S. One possible exception based on animal implantation studies might be the use of certain forms and types of nickel-containing alloys as orthopedic implants. However, the types and forms of nickel alloys actually used for human implantation (*e.g.,* stainless steel rods) have not shown evidence of carcinogenicity in animal studies and cannot reasonably be anticipated to be a human carcinogen via implantation or any other route of exposure.

We recommend that NTP consider the listing of implants as a separate category. Nevertheless, if NTP were to list certain nickel alloys in the 10th RoC, only the types and forms of nickel-containing alloys that have shown evidence of carcinogenicity in animal implantation studies should be listed as *reasonably anticipated to be human carcinogens by implantation.* If such a listing were made, NTP should clearly state in the RoC that this listing does not apply to other nickel alloys (*e.g.,* stainless steel) or to other routes of exposure.

I look forward to attending the upcoming meeting of the Board of Scientific Counselors Subcommittee in Washington. If you have any questions about the enclosed comments, please contact me.

Sincerely,

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

Enclosure

2605 Meridian Parkway, Suite 200, Durham, NC 27713
Telephone 1-919-544-7722 • Fax 1-919-544-7724

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

November 29, 2000

1. Summary

The Nickel Producers Environmental Research Association (NiPERA) is pleased to submit these Comments on the Draft Report on Carcinogens: Background Document for Metallic Nickel and Certain Nickel Alloys ("Background Document") for consideration by NTP's Board of Scientific Counselors. In the Background Document, NTP proposes to list both "Metallic Nickel" and "Certain Nickel Alloys" as "*reasonably anticipated*" human carcinogens. As discussed below, neither listing seems appropriate.

With respect to **Metallic Nickel**, the weight of evidence does not support a finding of "*reasonably anticipated*" human carcinogenicity:

- Epidemiological studies have not demonstrated an association (causal or otherwise) between exposure to metallic nickel and carcinogenicity. This negative finding has been consistent across numerous studies from various industry sectors. The studies have been of good quality and, in many instances, ample size. Moreover, while metallic nickel exposures in these studies generally were low, there were some notable exceptions.

- Metallic nickel exposures in current occupational settings are likely to be lower (and certainly not higher) than the exposures encountered in the above noted epidemiological studies. Hence, there is no reason to expect that occupational exposure to metallic nickel in any industry sector within the U.S. constitutes a risk factor for respiratory or other cancer.

- Metallic nickel is not found in food and water; and, at most, only trace amounts will be found in the ambient air (only a fraction of a nanogram per cubic meter). Pure metallic nickel implants are never used in the U.S. Hence, aside from potential dermal exposures that the general populace may experience through the use of nickel-plated articles such as watches and jewelry, exposures to metallic nickel will be negligible. With respect to dermal exposures, there are no epidemiological studies, clinical reports, or animal studies indicating an association between such exposures and increased risk of cancer.

- The only "positive" carcinogenic evidence for metallic nickel in animals is found in studies where the route of exposure is not of relevance to humans. Moreover, high mortality in some of those studies suggests that toxicity could have confounded the carcinogenic findings.

- 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.

- With this evidence, a "*reasonably anticipated*" human carcinogen listing for metallic nickel is not justified.

With respect to **Nickel Alloys**, the weight of evidence does not support a finding of "*reasonably anticipated*" human carcinogen either:

- 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 properties of a particular alloy depend on the content and nature of the metals present in the alloy and the alloy form. Among other things, these will largely determine the rate of release of metal ions under various environmental or biological conditions.

- Epidemiological studies have not demonstrated an association (causal or otherwise) between exposure to nickel alloys and carcinogenicity. This includes evidence from both occupational cohorts exposed by inhalation and patient populations with orthopedic implants made out of nickel-containing alloys.

- Only certain alloys in forms other than those used in human implants (*e.g.*, powders, fiber porous composites) have induced tumors in animals and, in those cases, the studies involved routes other than inhalation, oral, or dermal exposure. The types and forms of alloys used in medical or prosthetic devices (*e.g.*, stainless steels) have shown no evidence of carcinogenicity via implantation or other relevant routes of exposure in properly conducted studies.

- NTP, like IARC, should treat medical devices and implants as the subject of a separate carcinogenicity assessment. If, however, NTP chooses to address implants in the context of its evaluation of "Certain Nickel Alloys," a *reasonably anticipated human carcinogen* listing, if made at all, should be carefully limited to those types and forms of alloys for which evidence of carcinogenicity via implantation exists. Furthermore, NTP should make clear that any such listing does not apply to routes of exposure other than implantation.

Below are NiPERA's main comments on the proposed listings. References cited here and more detailed comments on the RoC Background Document can be found in Attachment 1.

2.0 Metallic Nickel

The evidence relating to the potential carcinogenicity of metallic nickel is unique when compared to all the other agents that the NTP has listed as *reasonably*

anticipated to be human carcinogens. First, it falls within a very limited subset of agents listed by NTP as "*reasonably anticipated*" carcinogens for which the animal evidence is not based upon relevant routes of exposure. Most (> 90%) of the 165 agents determined to be "*reasonably anticipated*" carcinogens by the NTP in the 9th RoC have shown some evidence of carcinogenicity in animals via drinking water, gavage, diet, inhalation or dermal exposure. In the few cases where an agent has been listed by NTP as *reasonably anticipated* to cause cancer without positive animal data by a relevant route of exposure, it appears that human evidence was either absent or suggestive of a causal association.

This is not true for metallic nickel. In fact, for metallic nickel, the animal evidence (albeit limited) via a relevant route of exposure—inhalation—has essentially been negative. More importantly, the epidemiological data consistently indicate that metallic nickel is not carcinogenic in humans. The metallic nickel exposures in the negative epidemiological studies were at least as high, or higher, than exposures encountered in the workplace today and orders of magnitude higher than metallic nickel concentrations in the ambient air. To the extent that the human data are viewed as "inadequate" to determine the carcinogenicity of metallic nickel one way or the other, the problem is not an inability to establish causality definitively where a positive association has been found. Instead, it is the inherent limitation of all negative epidemiological studies to absolutely "prove" that an agent poses no threat to human health under any circumstances. Moreover, the "positive" injection data reported in the RoC as supporting a "sufficient" finding of carcinogenicity in animals are of questionable relevance to evaluating potential human carcinogenicity given the artificiality of the routes of exposure for human hazard identification and the high mortality of animals in some studies. These data are discussed in greater detail below and in Attachment 1 to these Comments.

2.1 Metallic Nickel--Human Data

The Background Document states that IARC (1990) found inadequate evidence of carcinogenicity in humans for metallic nickel, citing small cohorts and low exposures as reasons why IARC could not reach a definitive conclusion regarding the lack of an association between exposures to metallic nickel and respiratory cancer. The Background Document further states that relatively little epidemiological evidence pertains to metallic nickel. While this may have been true at the time that IARC reached its conclusions in 1990, it is not true today.

Over 40,000 workers from various nickel-using industry sectors (nickel alloy manufacturing, stainless steel manufacturing, and barrier manufacturing) have been examined for evidence of carcinogenic risk due to exposure to metallic nickel and, in some instances, accompanying oxidic nickel compounds (Enterline and Marsh,1982; Cox *et al.,* 1981; Cragle *et al.,*1984; Arena *et al.,* 1998; Moulin *et al.,* 2000). No nickel-related excess respiratory cancer risks were found in any of these nickel-using industry workers. While it is true that metallic nickel exposures,

on average, were low (< 0.5 mg Ni/m^3, ranging up to averages of 1.5 mg Ni/m^3), the exposures were far higher than those found in the ambient air (negligible) and at least as high or higher than metallic nickel exposures found in occupational settings today. Thus, exposure levels and number of workers exposed (>40,000) were not inconsequential in those studies, lending strength to the belief that metallic nickel exposures of relevance to the general population or in occupational settings are not a cause for concern.

Studies of nickel-producing workers have also been negative. In a study of hydrometallugical refining workers, no nickel-related excess cancer risks were seen in 718 workers exposed to metallic nickel concentrations ranging from 0.2 to 49 mg Ni/m^3 (Egedhal *et al.,* 1993). A further update on this cohort by Egedahl and co-workers is expected to be published in the next few months in the Journal of Occupational and Environmental Medicine. This update, which undoubtedly will extend the person-years of follow-up for this cohort several-fold, still indicates lower than expected deaths for respiratory malignancies. Similarly, in a study of two refinery cohorts (~ 6,000 workers) cross-classified by cumulative exposure to various nickel species, no evidence of increased lung or nasal cancer risks associated with metallic nickel was found (ICNCM, 1990). Exposures to metallic nickel in some departments within these refineries were > 5 mg Ni/m^3.

Thus, although the number of workers generally exposed in refinery studies (several thousand workers per study) is relatively small compared to the number of workers exposed in nickel-using industry studies (in the main, ranging from several thousand to ~32,000 workers), metallic nickel exposures of the refinery workers were higher (in many cases, much higher) than any occupational exposures to metallic nickel found in U.S. industries. Yet no excess metallic nickel-related cancer risks have been seen in these workers. This can be contrasted to observed excess respiratory cancer risks in a much smaller cohort of refinery workers (343) exposed almost solely to sulfidic nickel at levels similar to those found in the above noted refinery workers exposed to metallic nickel (1-5 mg Ni/m^3) (ICNCM, 1990). See Attachment 1, Part A, Section 3.

The Background Document discusses the potential exposure to metallic nickel through prostheses and implants. The fact is, however, that people in the U.S. are not exposed to implants made out of pure metallic nickel; hence, discussions of implants are of relevance only to nickel alloys (see Section 3 below).

Finally, with respect to general population exposure, it should be noted that metallic nickel is not found in food or water; and, at most, only trace amounts (a fraction of a nanogram/m^3) will be found in the ambient air. As noted above, pure metallic nickel implants are never used in the U.S. Hence, aside from potential dermal exposures that the general populace may experience through the use of nickel-plated articles such as watches and jewelry, exposures to metallic nickel will be negligible. In addition, there are no epidemiological studies, clinical reports, or animal studies

indicating an association between dermal exposures to metallic nickel and increased risk of cancer[1]. The only hypothetical scenario in which metallic nickel theoretically could present a carcinogenic risk would be by implantation of pure metallic nickel. But that scenario does not exist, since implants are not made out of pure metallic nickel as opposed to nickel-containing alloys.

2.2 Metallic Nickel--Animal Data

The animal data cited in the Background Document as evidence of the carcinogenicity of metallic nickel must be carefully examined relative to the criteria used by NTP to establish the "sufficiency" of carcinogenic evidence in animals. As noted above, evidence for the carcinogenicity of metallic nickel in animals arises solely from studies involving non-relevant routes of exposure for humans (*i.e.,* routes other than inhalation, oral, or dermal exposure). Moreover, suggestive evidence of toxicity in some of these studies (Ivankovic *et al.,* 1988; Pott *et al.,* 1987; 1992) may partially confound the carcinogenic "findings," thereby calling into question whether carcinogenicity has, indeed, been demonstrated in multiple species. By contrast, early inhalation studies in animals, although limited, suggest that metallic nickel does not induce malignant tumors in animals when administered through a relevant route of exposure (see Attachment 1)[2].

As a general rule, NTP has required some evidence of carcinogenicity in animals via inhalation, oral, or dermal routes of exposure before listing an agent in the RoC. The absence of positive data from relevant routes of exposure for metallic nickel, combined with the considerable epidemiological evidence that exposure to metallic nickel does <u>not</u> result in excess cancer risks, argues strongly against listing metallic nickel as "*reasonably anticipated to be a human carcinogen*." These issues are discussed in greater detail in Attachment 1, Part A, section 4.1.

3.0 Nickel Alloys

NiPERA's major concerns with the **Nickel Alloy** sections of the Background Document are two-fold. First, the data clearly do not support listing an undefined category of "Certain Nickel Alloys" as *reasonably anticipated human carcinogens.* Any such broad categorical listing would be very problematic, since each type of nickel-containing alloy is a unique substance with its own special physico-chemical

---

[1] Issues related to allergic contact dermatitis have prompted the European Union to adopt regulations (Nickel Directive) that restrict nickel release rates from objects in direct and prolonged contact with the skin. This initiative that eliminates the use of nickel plated jewelry is supported by NiPERA. If the U.S. adopts similar regulations in the future, dermal exposures to nickel plated objects will essentially cease to exist.

[2] NiPERA is overseeing the conduct of a two-year inhalation cancer bioassay with elemental nickel powder in male and female Wistar rats which is expected to be completed in 2004. An OECD-compliant protocol is being used in the study, with supplemental lung burden analyses to assure absence of impaired lung clearance.

and biological properties that differ from those of its individual metal constituents and other alloys (see Attachment 1, Part B). Among other things, differences in the nature of the metals present in the alloys result in different metal ion release rates in environmental and biological media. Second, while it may be reasonable to anticipate some increased cancer risk via implantation for certain alloys in particular forms (*e.g.,* powders), those alloys cannot *reasonably be anticipated to be a human carcinogen* by other routes of exposure, and they are not used in human orthopedic implants. Specific detailed comments are presented below.

3.1 Nickel Alloys—Human Data

The Background Document is correct in noting that there are no studies of nickel workers exposed solely to nickel alloys. Clearly, however, workers in alloy and stainless steel manufacturing and processing do have low level nickel alloy exposures. Studies on stainless steel and nickel alloy workers have shown no occupationally related excess risks of cancer (Cornell, 1984; Moulin *et al.,* 1993, 2000; Svensson *et al.,* 1989; Jakobsson *et al.,* 1997; Hansen *et al.,* 1996; Arena *et al.,* 1998; Cox *et al.,* 1981). Some of these studies involved thousands of workers; the Arena *et al.* (1998) study comprised >31,000 workers. (See Attachment 1.) Hence, the absence of excess cancer risks in these workers strongly indicates that such occupations do not constitute a risk factor for cancer.

With respect to implant exposures, 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). Of the fourteen cohort studies which have been performed to investigate cancer incidence in patients following total knee or hip replacements, only one study has shown a small increase in overall cancer incidence (Nyren *et al.,* 1995; McGregor *et al.,* 2000). (See Attachment 1, part B, section 3.) And, as the recent IARC monograph evaluating carcinogenic risks associated with surgical implants and other foreign bodies noted, in the few studies where excess lympho-hematopoietic cancers have been observed, there was no information on possible confounding variables, such as immunosuppressive therapy or rheumatoid arthritis (IARC, 1999; McGregor *et al.,* 2000). Thus, while there may be some difficulties in interpreting the cohort studies (*e.g.,* accounting for a healthy patient effect, limited follow-up), the epidemiological data, as the Background Document points out, generally suggest that there is little excess risk associated with orthopedic implants.

Aside from occupational inhalation and medical implant exposures, the only other route of exposure to nickel alloys that could be of concern to humans is dermal exposure, since general population exposure to nickel alloys in air, water or food will be negligible to non-existent. With respect to dermal exposures, the general population has contact with massive forms of nickel-containing alloys in the form of 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. Yet, there have been no epidemiological or clinical reports of an association between dermal exposure to massive forms of nickel-containing alloys and increased risk of cancer. Indeed, the nickel alloys to which humans have substantial dermal exposure will not even provoke an allergic skin response (let alone cancer) in nickel-sensitized individuals. See Attachment 1, Part B, Section 2.

3.2 Nickel Alloys—Animal Data

NTP's proposed classification of "**Certain Nickel Alloys**" as *reasonably anticipated human carcinogens* is based solely on animal data and appears to apply to certain alloys of high nickel content (*e.g.,* alloys with more than 50% nickel) in particular forms (*e.g.,* powders, fiber porous composites). See Background Document page 51. While there are concerns with some of these alloy studies due to poor survival (indicative of toxicity), studies using the implantation route of exposure have more relevance for humans in the case of alloys than in the case of metallic nickel, since humans can be exposed to nickel alloys via the use of prosthetic devices. However, the alloys that tested positive via implantation in animals had a high nickel content and/or were present in forms (*e.g.,* powders) not used in human prosthetic devices. By contrast, the types and forms of nickel alloys actually used for human implantation (*e.g.,* stainless steel rods) have not shown evidence of carcinogenicity in animal studies and cannot reasonably be anticipated to be a human carcinogen via implantation or any other route of exposure.

4.0 Weight of Evidence Determination Regarding the Listing of Metallic Nickel and Certain Nickel Alloys in the 10th RoC

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.

Applying these criteria to the overall weight of the evidence for **Metallic Nickel** and **Nickel Alloys**, it is clear that these forms of nickel should not be listed as *reasonably anticipated human carcinogens* in the Tenth RoC because: (1) There is no evidence from human studies of increased cancer risk associated with metallic nickel or nickel alloy exposures (to the contrary, epidemiological studies indicate the absence of an increased cancer risk); and (2) the only animal studies showing evidence of a tumorigenic response involved non-relevant routes of exposure with metallic nickel and certain nickel alloy powders, or implantation of foreign bodies generally made out of alloys with a high nickel content and in forms (*e.g.,* powders, porous composites) that are not used for human implants. By contrast, there is no evidence of carcinogenicity for metallic nickel or nickel alloys via inhalation, ingestion, or dermal exposure in humans or animals. Accordingly, there is no basis for "*reasonably anticipating*" that either metallic nickel or nickel-containing alloys as a class are carcinogenic to humans via a route that is relevant to the potential exposures of persons residing in the United States.

At the same time, some animal studies give evidence of tumorigenic activity associated with implanted foreign bodies made of certain alloys (*e.g.,* high nickel content alloys) in particular forms (*e.g.,* powder, fiber porous composite). NiPERA believes "implants" should be subject to a separate carcinogenicity assessment by NTP, as they are by IARC. If, however, NTP chooses to address implants in the context of its evaluation of "Certain Nickel Alloys," a *reasonably anticipated human carcinogen* listing should be carefully limited to **those types and forms of alloys for which evidence of carcinogenicity via implantation exists.** Any such listing also should make clear that (1) it does not apply to routes of exposure other than implantation; and (2) it does not apply to other nickel alloys (*e.g.,* stainless steel) even when used in implants. NTP also should inform readers of the Background Document and the RoC that nickel alloys of the type covered by the listing are not used in surgical or orthopedic implants. These limitations and caveats are critically important—because without them, listing "Certain Nickel Alloys" as *reasonably anticipated human carcinogens* would send an alarming and scientifically unwarranted message to hundreds of thousands of implant wearers that they can

expect to get cancer in the future from their implants. It also could deter thousands of others from undergoing medically appropriate and highly beneficial implantation procedures for no good reason.

Attachment 1

Comments of the Nickel Producers Environmental Research Association on the National Toxicology Program Draft RoC Background Document for Metallic Nickel and Certain Nickel Alloys

November 29, 2000

Table of Contents

Page
INTRODUCTION 3
PART A. COMMENTS ON METALLIC NICKEL 3
Section 2. Human Exposure (page 9 of the Background Document) 3
Section 3. Human Cancer Studies (page 33 of the Background Document) 3
Section 4.1 Studies of Cancer in Experimental Animals (Metallic Nickel, pages 37 to 43 of the Background Document) 5
Section 5. Genotoxicity (page 53 of the Background Document) 6
Section 6. Other Relevant Data (Page 61 of the Background Document 9
Discussion of IARC Classification of Metallic Nickel (pages 33 and 37 of the Background Document) 9
PART B. COMMENTS ON NICKEL-CONTAINING ALLOYS 11
Section 2. Human Exposure (page 9 of the Background Document) 12
Section 3. Human Cancer Studies (page 33 of the Background Document) 13
Section 4.2 Studies of Cancer in Experimental Animals (Nickel Alloys, pages 43 to 49 of the Background Document) 16
Discussion of IARC Classification of Nickel Alloys (pages 33 and 37 of the Background Document) 18
REFERENCES 18

INTRODUCTION

These comments pertain to NTP's 2000 Draft Report on Carcinogens (RoC) Background Document on Metallic Nickel and Certain Nickel Alloys, referred to hereinafter as "Background Document." In the Background Document, metallic nickel and nickel-containing alloys are not discussed separately. Instead, the toxicological data for metallic nickel, some nickel compounds, and nickel alloys are discussed together within the various sections. The comments below are divided into parts A and B. Part A includes comments mostly pertaining to Metallic Nickel and Part B contains comments corresponding to Nickel-Containing Alloys. Within each of these parts, NiPERA's comments are arranged so as to correspond with the sections and page numbers given in the Background Document.

PART A. COMMENTS ON METALLIC NICKEL

SECTION 2. HUMAN EXPOSURE (PAGE 9 OF THE BACKGROUND DOCUMENT)

The section on Biological Indices (page 24) is very sketchy. It fails to inform the reader that the main problem with biological indices is that their value as a marker of exposure is dependent on the nature of the nickel-containing substance to which a person is exposed. Air exposure levels of water insoluble nickel compounds do not correlate well with corresponding serum and urinary nickel levels while exposures to water soluble nickel compounds do.

SECTION 3. HUMAN CANCER STUDIES (PAGE 33 OF THE BACKGROUND DOCUMENT)

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-of which there are none in the U.S. No nickel-related excess respiratory cancer risks have been found in any nickel-using industry workers.

The RoC states that relatively little epidemiological evidence pertains specifically to metallic nickel and that relatively few workers have been exposed to this form of nickel. This is not true. The ICNCM study analyzed data from refinery cohorts (~6,000 workers) cross-classified by cumulative exposure and found no evidence of increased lung or nasal cancer risks associated with <u>metallic nickel</u> exposure. Likewise, in an update study of 1,649 hydrometallurgical refinery workers in Canada, no excess lung or nasal cancers deaths were reported (Egedahl *et al.,* 1993). Although the number of exposed workers in the cohort was small (715), exposures in this plant were solely to nickel concentrates and metallic nickel. Exposure ranged from 70 to 700 mg metallic Ni dust/m^3 in the earlier operating period. Metallic dust levels in the metals recovery area and rolling mill areas ranged from 0.3 to 49 mg Ni/m^3 and 0.2 to 14 mg Ni/m^3 respectively. A further update on this cohort by Egedahl and co-workers is expected to be published in the next few months in the Journal of Occupational and Environmental Medicine. This update, which will undoubtedly extend the person-years follow-up of this cohort several-

fold, still indicates lower than expected deaths for respiratory malignancies (Egedahl, personal communication).

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). 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 and a range of up to 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."

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). No occupationally related excess respiratory cancer mortality was seen among these workers. Average nickel exposures (consisting of oxidic nickel and dusts containing metallic nickel and nickel alloys) were estimated to range from 0.01-0.3 mg Ni/m^3, with a median value of 0.08 mg Ni/m^3. Of particular interest are the data from the powder metallurgy department (where exposures would likely have been solely to metallic nickel); average exposure estimates of 1.5 mg/m^3 of elemental nickel were reported. The workers in this department, albeit small in size, showed no nickel-related excess cancer risks. 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.

In section 3.2 Nickel compounds, the Background Document states that two well conducted epidemiological studies of workers exposed to nickel showing no excess respiratory cancer risk should be considered uninformative due to their small size (<300 workers). Given the above discussion, it is unclear what two studies the Background Document is referring to. Yet on page 34, two questionable studies of self reported exposures for patients with salivary gland (Horn-Ross *et al.,* 1997) and laryngeal (Wortley *et al.,* 1992) tumors are discussed as evidence for the carcinogenicity of "generic nickel."

In sum, data from a significant number of workers (over 40,000) exposed to metallic nickel powders do not indicate an increased risk of respiratory cancer. The only possible criticism of the available epidemiological data for metallic nickel is that, even in the past, mean exposures to metallic nickel have generally been low ($\leq$ 1 mg Ni/m^3) compared to exposures to various nickel compounds. However, since these exposures are as high or higher than those expected to be found currently for U.S. workers, the negative epidemiological data for metallic nickel are quite relevant to the RoC listing consideration for metallic nickel. This observation applies with even greater force in the case of general population exposures, which are several orders of magnitude below occupational levels.

Finally, 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.

SECTION 4.1 STUDIES OF CANCER IN EXPERIMENTAL ANIMALS (METALLIC NICKEL, PAGES 37 TO 43 OF THE BACKGROUND DOCUMENT)

Animal data often help to elucidate mechanisms of carcinogenesis or to provide perspective on epidemiologic results that are equivocal or confounded by other exposures. 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.

The interpretation of early inhalation studies by Hueper and collaborators is limited by the high exposures (15 mg/m^3), high mortality, high respiratory toxicity, and lack of proper controls in these studies. In one instance where 100% of the animals died prior to the completion of the study and toxicity was evident in respiratory and liver tissue, guinea pigs showed pre-neoplastic lesions in the lungs; while under the same exposure conditions mice did not (Hueper, 1958). In another study, hamsters experiencing somewhat lower mortality and toxicity did not show the induction of respiratory tumors. In one study (Hueper, 1958), rats experiencing high mortality and high respiratory toxicity showed benign pre-neoplastic lesions while in a follow-up study in which mortality and lung toxicity were somewhat reduced, no induction of respiratory tumors was seen (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^0 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 hamsters (Ivankovic *et al.,* 1988), the authors state that significant increases in percent of animals with malignant tumors compared to controls were observed at a total cumulative dose of 40 mg but not 10 or 20 mg Ni/animal of nickel powder. When the authors analyzed the malignant tumors by site, some of these tumors were considered to be nickel-related (*i.e.,* not found in control animals). However, the location of the so-called nickel-related tumors (mediastinum, pleura, cervix) is suspect since it does not correspond to the classical tumor sites induced by Ni subsulfide in the rat NTP inhalation study (NTP, 1996). It should be noted that significant mortality was present in the Ivankovic study (survival time of 241 to 340 days compared to 500-544 days for controls). 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).

Since there is evidence of high mortality (and possibly high respiratory toxicity) in the Ivankovic study, the significance of this study for hazard identification is questionable. The problems involved with evaluating carcinogenic responses in animals exhibiting high toxicity have long been noted (Griesemer and Cueto, 1980; Cohrssen and Covello, 1989). It should also be noted that the relevance of intratracheal instillation as a route of administration for humans is highly questionable, in particular when the target organ is the lung. Recently, Driscoll *et al.* (2000) cautioned that, particularly in the case of intratracheal instillation studies, care must be taken to avoid doses that are excessive and may result in immediate toxic effects to the lung due to a large bolus delivery. Instillation produces heavier and more centralized particle deposition than inhalation. 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; Rigaut, 1983; Sunderman, 1984; Sunderman *et al.,* 1984; Jasmin and Riopelle, 1976; Pott *et al.,* 1987; Sunderman, 1989; Muhle *et al.,* 1992). With regard to injection studies, Pott *et al.* (1987; 1992) noted the limitations of their i.p. tests stating that "certainly, intraperitoneal injection of dusts is a nonrealistic exposure route" and that "an i.p. test cannot simulate the selection of particles which occurs physiologically after inhalation by deposition in different parts of the airways and by clearance mechanisms."

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. 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 that 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 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. Only inhalation studies should be considered for respiratory hazard assessment, since only these studies can account for all the factors that can ultimately determine the respiratory carcinogenic potential of a given nickel-containing substance.

In sum, inhalation studies with metallic nickel powder have not shown a clear nickel-related carcinogenic response, and no animal studies 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 questionable routes of exposure, and in some cases high mortality suggestive of toxicity.

SECTION 5. GENOTOXICITY (PAGE 53 OF THE BACKGROUND DOCUMENT)

The introduction to this section in the Background Document states that the data presented in Section 5 have an emphasis on nickel metal and alloys. It seems reasonable in the context of a background document on metallic nickel and nickel alloys to focus just on these substances, with references to nickel compounds only for comparison purposes. Alternatively, all the available data for all nickel compounds, metallic nickel and nickel alloys could be presented if a comprehensive review is desired. What the Background Document has done however, is to selectively pick certain studies with nickel compounds (of questionable relevance for metallic nickel) with no explanation or rationale for this selection. For example, Subsection 5.2.1. *Micronucleus formation in Tradescantia and Vicia*, reports results with nickel chloride only. Subsections 5.3.1.*1 Lac I mutation in transgenic rat embryonic fibroblasts*, 5.3.1.3 *DNA single-*

strand breaks in mouse lung and nasal mucosa cells (comet assay), 5.3.3.1 *Lac Z and Lac I mutations in transgenic rodents*, and 5.3.2.2 *DNA single-strand breaks in rodents lung and nasal mucosa* pertain to nickel subsulfide only.

The transgenic animal study with nickel subsulfide (Mayer *et al.,* 1998) is extensively reviewed in the Background Document. In this study, Muta ™ Mice and Big ™ Blue rats were exposed by inhalation to a very high concentration of Ni subsulfide (close to MTD, 24-352 mg Ni subsulfide/m^3 during 2 hours). The results of this study showed a lack of mutagenicity in nasal or lung tissues, in rats or mice after *in vivo* inhalation of nickel subsulfide particles. DNA damage was demonstrated in nasal and to a lesser extent in lung tissue from mice exposed by inhalation to nickel subsulfide but not in rats. By contrast, *in vitro* exposures to nickel subsulfide resulted in increased *lacI* mutant frequencies in rat fibroblast cells and enhanced DNA damage in nasal and lung primary cells from mice. Mayer and co-workers conclude: "*There are remarkable differences in the potency of carcinogenic Ni subsulfide to induce genotoxic and mutagenic endpoints depending on whether these effects are studied in vitro or in vivo.*" This statement is perhaps the only conclusion from this study relevant for the case of metallic nickel or nickel alloys and supports the contention that only inhalation studies can account for all the factors that determine the ultimate respiratory carcinogenic potential of a nickel-containing substance.

The reminder of the studies presented in this section discuss results obtained with metallic nickel powders (Ni^0), alloy extracts (Ni^{2+} and other metal ions) and welding fumes (complex nickel spinels). All these studies appear relevant to evaluate the genotoxicity of metallic nickel and nickel alloys. However, it should be noted that the studies with alloy extracts are interesting but limited by the fact that only ionic uptake into cells can be measured using extracts. Studies with particles of metallic nickel or alloys may be more appropriate since they allow for the test material to be taken up by phagocytosis.

One such study with metallic nickel powder is the one by Costa *et al.* (1981) reported in section 5.3.1.4 (page 55) of the Background Document. In this study, particles of nickel metal powder and particles of various nickel compounds are used to induce morphological transformation of cultured SHE cells. The Background Document reports that some transformation (3%) was seen at the highest exposure level of metallic nickel powder. Costa's conclusion based on all the results obtained was that "*metallic nickel did not induce significant transformation in the present study.*" Indeed, at the same concentration of powder, Ni subsulfide (70% nickel, 30% sulfur) induced a 30-fold higher percent of cell transformation than metallic nickel powder (100% nickel) of similar particle size. These results point out the differences in bioavailability of Ni^{2+} ion from these two nickel-containing substances. Nickel powder did not induce chromosomal aberrations in human peripheral lymphocytes in culture (Paton and Allison, 1972).

In section 5.3.1.5 of the Background Document, Costa *et al.* (1982) is the wrong reference for powder nickel blocking progression through cell cycle. The correct reference is Costa *et al.*, 1983. In this study, powder metallic nickel was the least potent of all the tested materials ($CdCl_2$, $HgCl_2$, $CoCl_2$, $NiCl_2$, $ZnCl_2$, $CuSO_4$, $PbSO_4$, As, Ni_3S_2, NiS, Ni_3Se_2, NiO) at inducing cell cycle arrest in CHO cells.

In Section 5.3.2.3 (page 57) of the Background Document, chromosomal aberrations (CA) in human bone marrow cells of patients with prostheses are reported. In the study by Case and co-workers, (1996), chromosomal aberrations are measured in femoral bone marrow cells adjacent to metal prosthesis in patients undergoing a replacement of these prostheses. Metal

ion concentrations in the vicinity of the old implants were increased several hundred fold compared to no-implant controls (mean values increased 6,700-fold for Cr, 850-fold for Co and 580-fold for Ni), although the exact composition of the alloys was not reported. Even with such high increases in metal ions, particularly Cr, chromosomal aberrations were 8% in revision patients compared to 4% in controls. Only chromatid breaks were found to be elevated. Chromosomal aberrations in bone marrow from non-adjacent sites were not different from controls. The significance of these results with regard to presence or absence of implant site tumors and possibility of hematopoetic malignancies is not known at this time. The Background Document needs to be much more careful about its interpretation of these data.

Cytogenetic abnormalities (CA, SCE, MN) measured in peripheral blood cells are receiving a lot of attention as possible biomarkers of effect associated with carcinogenic risk. Hagmar *et al.* (1998) explored the predictivity of these biomarkers by analyzing CA (chromosomal aberrations), SCE (Sister Chromatid Exchange) and MN (Micronuclei) in blood taken from 3,541 subjects in Norway and Italy. The results in each category were divided into three percentiles (low, medium, high). The Nordic cohort had 1.5 SMR for all cancers in subjects with "high" CA frequency in peripheral blood lymphocytes. The Italian cohort had SMR of 2.0 for all cancers in subjects with "high" CA frequency. These results were not affected by gender, age, and time since test. No association was found between SMR and "high" MN or SCE. The authors speculate that CA may reflect either early biological effects of genotoxic carcinogens or individual cancer susceptibility (polymorphism of metabolizing enzymes may influence CA).

There are several studies of nickel-exposed workers in which CA and SCE were measured in peripheral blood. Waksvik and co-workers (Waksvik and Boysen 1982) looked for CA and SCE in blood samples from 19 exposed nickel refinery workers and 7 controls, all non-smokers. Gaps, but not chromosome breaks or SCE, were significantly elevated in the exposed groups, even though plasma nickel levels were 4- to 5-fold higher in the exposed groups compared to controls. Furthermore, gaps and breaks were elevated in a group of 9 retired refinery workers with more than 25 years of exposure compared to 11 controls (Waksvik *et al.,* 1984). The frequencies of SCE were similar for exposed and control retired workers.

More recently, Senft *et al.* (1992) detected a significant increase in CA in blood samples from workers involved in the manufacturing of nickel sulfate and nickel oxide. The control group had an average CA of 4.05 ± 2.27, and the exposed group 6.41 ± 1.90. No correlation between CA and nickel in serum or urine was found. In another recent study (Gennart *et al.,* 1993), metal powder workers with exposure to nickel, chromium, iron and cobalt showed elevated values of SCE in peripheral blood samples. Again, no dose-response with duration of employment or urinary metal levels was found, while smoking influenced the results. Studies of steel welders exposed to fumes containing complex nickel spinels, chromium and other metals have not consistently showed an association between SCE and/or CA and welding of stainless steel (Werfel *et al.,* 1998; Popp *et al.,* 1991; Knudsen *et al.,* 1992; Jelmert *et al.,* 1995)

It should be noted, that CA, SCE and MN are assays that detect non specific chromosomal damage that occurred in lymphocytes circulating in peripheral blood. There are many factors that can influence the formation of CA, SCE and MN in peripheral lymphocytes. For example, caffeine and alcohol consumption, smoking, age, exposure to radiation, solvents, other metals,

etc[1]. In addition, chromosomal damage in peripheral lymphocytes does not necessarily reflect the damage experienced by the epithelial respiratory cells that may be indicative of increased risk for respiratory cancer (the only tumor site consistently associated with nickel exposures by relevant routes). In summary, a lack of elevation in the CA, SCE and MN does not necessarily mean lack of risk for respiratory cancer while the elevation of these values does not necessarily mean increased risk due to nickel exposures. So far there has been no validation of a relationship between blood nickel and lymphocyte damage. Furthermore, there is no validation between lung respiratory risk and damage to peripheral lymphocytes.

SECTION 6. OTHER RELEVANT DATA (PAGE 61 OF THE BACKGROUND DOCUMENT

In Section 6.1.2 of the Background Document, it should be made clear that when particles containing nickel are taken up by cells via phagocytosis/endocytosis, these particles may aggregate around the nucleus but do not migrate as such into the cell nucleus. Only the metal ions dissolved from these particles can migrate and or accumulate in the nucleus (Costa *et al.,* 1982).

DISCUSSION OF IARC CLASSIFICATION OF METALLIC NICKEL (PAGES 33 AND 37 OF THE BACKGROUND DOCUMENT)

On pages 33 and 37, the Background Document reports that in 1990 IARC classified metallic nickel as a possible human carcinogen (Category 2B) based on positive animal injection studies and inadequate human data. Since that time, however, additional studies of large cohorts of nickel alloy and stainless steel workers have reported no significant increase in respiratory cancer risk associated with inhalation exposure to metallic nickel dusts (see above discussion, Egedahl *et al.,* 1993; Arena *et al.,* 1998; Moulin *et al.,* 2000). The more recent epidemiological studies added tens of thousands of workers to the original data set and showed no association between exposure to metallic nickel dusts and excess respiratory cancer risk.

Other carcinogenic evaluations by regulatory and quasi-regulatory bodies should also be considered in the Background Document. 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

[1] Other exposures/factors that can affect the levels of chromosomal alterations include: ethylene oxide, styrene, benzene, arsenic, chloromethylether, chloropropene, organophosphates, ionizing radiation, pesticides, medicines, vitamins, iron, cobalt, arsenic, and chlorinated solvents.

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 (IARC, 1999). Among their recommendations, the group indicated that implanted foreign bodies consisting of pure metallic nickel should be classified as Category 2B *(possibly carcinogenic to humans)* (McGregor *et al.,* 2000). This assessment appears well founded. However, it should be noted that people in the U.S. are not exposed to implants made out of pure metallic nickel, so IARC's recommendation on this point does not appear relevant to NTP's evaluation.

PART B. COMMENTS ON NICKEL-CONTAINING 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 carcinogenicity of a nickel alloy must, therefore, be evaluated separately from the potential carcinogenicity of nickel metal itself and other nickel-containing alloys, 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. For a given concentration of nickel in an alloy, the presence of other metals can increase or decrease the corrosion rates (*i.e.,* metal ion release) under environmental or biological conditions.

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. 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 and this resistance is dependent on the nature of the metals as well as the proportion of the metals present in the alloy.

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, 1999). 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 or alloys of different composition.

SECTION 2. HUMAN EXPOSURE (PAGE 9 OF THE BACKGROUND DOCUMENT)

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 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 0.03 $\mu g/cm^2$/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-sensitised subjects even when in prolonged and intimate contact with the skin (Menné *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, certainly not cancer. 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.

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).

SECTION 3. HUMAN CANCER STUDIES (PAGE 33 OF THE BACKGROUND DOCUMENT)

There are no epidemiologic studies where exposures are only to powders of nickel-containing alloys. In studies of cohorts of high nickel alloy workers (where exposures included nickel alloy dusts as well as oxidic and elemental nickel species) 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).

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 from 13 plants were examined for excess risks of cancer (Arena *et al.,* 1998). The workers (exposed to mixtures of oxidic nickel and dusts containing metallic nickel and nickel alloys) were compared with local populations in geographic proximity to the plants (in order to control for geographic variation in mortality) and to the total U.S. population. Each of the plants studied was located in a metropolitan area and local populations were defined by established SMSAs (Standard Metropolitan Statistical Areas). The nickel worker population comprised only about 0.2 % of the SMSAs. No significant excess risk of respiratory cancer was found in comparison to local populations. A small excess risk of lung cancer (13%) was found in comparison to the U.S. population. However, there was no observed dose response with duration of employment or length of time since first employment, and the authors concluded that this small excess risk could be explained by some confounding factor, such as cigarette smoking.

Moulin and collaborators (Moulin *et al.,* 1990; Moulin *et al.,* 1993) 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.,* 1993). 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.

During the processing of stainless steel in such operations as grinding and welding, workers are exposed mostly 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.

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.

Subsection 3.3 of the Background Document addresses prosthetic implants. 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 of alloy implants) 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; Case *et al.,* 1994). 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).

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).

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). Likewise, 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.

SECTION 4.2 STUDIES OF CANCER IN EXPERIMENTAL ANIMALS (NICKEL ALLOYS, PAGES 43 TO 49 OF THE BACKGROUND DOCUMENT)

Very sparse animal data are available to evaluate the respiratory carcinogenicity of nickel alloys. 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.

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). The incidence of non implant site malignancies was not significantly different for animals receiving nickel-containing alloys (1/26 to 5/26) and sham operated controls (4/26). Implantation-site sarcomas were observed in 1/26 animals implanted with a Co-based alloy powder, 3/32 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. 35% Ni), and CoCrWNi alloys (12.4% Ni) 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, low corrosion) and a high nickel content alloy (96% nickel, high corrosion) 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 almost pure nickel 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. It should be noted that humans have been exposed to nickel-plated or nickel alloy jewelry (*e.g.,* earrings) for many years without any reports of tumors associated with this use.

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 <u>clinically-relevant alloys</u> 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. Positive animal tumor data are found only associated with injection or implantation of certain forms and types of nickel-containing alloys that are not used in medical implants.

DISCUSSION OF IARC CLASSIFICATION OF NICKEL ALLOYS (PAGES 33 AND 37 OF THE BACKGROUND DOCUMENT)

A separate carcinogenic assessment and listing for "implants" 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, Co-based, and Ti-based alloys) were not classifiable as to their carcinogenic potential to humans, *i.e.,* they were classified as Group 3 carcinogens (IARC 1999; 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, IARC recommended that implanted foreign bodies consisting of metallic nickel and one specific alloy powder (66-67% nickel, 13-16% chromium, and 7% iron) be classified 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.

REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH). 1999. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

Accominotti, M., Bost, M., Haudrechy, P., Mantout, B., Cunat, P. J., Comet F., Mouterde, C., Plantard, F., Chambon, P., Vallon, J. J. 1998. Contribution of chromium and nickel enrichment during cooking of foods in stainless steel utensils. Contact Derm. 38: 305-310.

Arena, V. C.; Sussman, N. B.; Redmond, C. K.; Costantino, J. P. and Trauth, J. M. 1998. Using alternative comparison populations to assess occupation-related mortality risk. J. Occup. Environ. Med. 40: 907-916.

ASM Specialty Handbook: Stainless Steels, 1994. J. R. Davis, ed., ASM International, Materials Park, OH, pp.4-5.

ATSDR 1997 Toxicological Profile for Nickel.

Carter, S. (Laboratory of the Government Chemist, UK) Report to the Nickel Development Institute, 9 November 1999.

Case, C. P.; Langkamer, V. G.; James, C.; Palmer, M. R.; Kemp, A. J.; Heap, P. F.; Solomon, L. 1994. Widespread dissemination of metal debris from implants. J. Bone Jt. Surg. 75-B: 701-712.

Case, C. P.; Langkamer, V. G.; Howell, R. T.; Webb, J.; Standen, G.; Palmer, M.; Kemp, A.; Learmonth, I. D. 1996. Preliminary observations on possible premalignant changes in bone marrow adjacent to worn total hip arthroplasty implants. Clin. Orthop. S269-279.

Cohrssen, J.J.; Covello, V. 1989. Risk Analysis: A Guide to Principles and Methods for Analyzing Health and Environmental Risks. U. S. Council on Environmental Quality. NTIS, Springfield, VA. NTIS publication number PB89-137772.

Coleman, M.P. 1996. Cancer risk from orthopedic prostheses. Ann. Clin. Lab. Sci. 26 (2): 139-146.

Cornell, R. G. 1984. Mortality patterns among stainless steel workers. Nickel in the Human Environment. IARC Scientific Publication No. 53, pages 65-71.

Costa 1991. Molecular mechanisms of nickel carcinogenesis. Ann. Rev. Pharmacol Toxicol. 31: 321-37.

Costa, M.; Cantoni, O.; de Mars, M.; Swartzendruber, D. E. 1983. Toxic metals produce an S-phase-specific cell cycle block. Res. Commun. Chem. Pathol. Pharmacol. Vol 38: 405-419.

Costa, M.; Heck, J. D.; Robinson, S. H. 1982. Selective phagocytosis of crystalline metal sulfide particles and DNA strand breaks as a mechanism for the induction of cellular transformation. Cancer Res. 42: 2757-63.

Costa, M.; Abbracchio, M. P.; Simmons-Hansen, J. 1981. Factors influencing the phagocytosis, neoplastic transformation and cytotoxicity of particulate nickel compounds in tissue culture systems. Toxicol. Appl. Pharmacol. 60: 313-323.

Cox, J. E., Doll, R., Scott, W. A., Smith, S. 1981. Mortality of nickel workers: Experience of men working with metallic nickel. Br. J. Ind. Med., 38: 235-239.

Cragle, D. L., Hollis, D. R., Newport, T. H., Shy, C. M. 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; pp. 57-63. (IARC scientific publications no. 53).

CRECEP 2000. Co-normative research on test methods for materials in contact with drinking water: metallic materials. Final Report. January 2000. CRECEP, 156 avenue Paul-Vaillant Couturier, 75014 Paris, France.

Donachie, M. 1998. Biomaterials. In: Metals Handbook, Desk Edition. Ed. Davis J. R., Davis & Associates. Pages 702-709.

Driscoll, K. E., Costa, D. L., 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. Toxicolog. Sciences, 55: 24-35.

EC 1999b. European Commission Communication of 20 July 1999, published in the Official Journal of the European Cmmunities: volume C 205, p5.

Egedahl, R. D., Carpenter M, Hornik, R. 1993. An update of an epidemiology study at a hydro metallurgical nickel refinery in Fort Saskatchewan, Alberta, Health Reports, Statistics Canada 5:293-302.

Enterline, P. E., Marsh, G. M. 1982. Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. J. Natl. Cancer Inst., 68: 925-933.

EPA 1986. Health Assessment Document for Nickel and Nickel Compounds (Final Report, September 1986. Pages 8-113.

Flint, G. N. and Packirisamy, S. 1997. Purity of food cooked in stainless steel utensils. Food Add. Contam. 14: 115-126.

Furst, A. and Schlauder, M. C. 1971 The hamster as a model for metal carcinogenesis. Proc. West. Pharmacol. Soc. 14: 68-71.

Gaechter, A.; Alroy, J.; Andersson, G.B.J.; Galante, J.; Rostoker, W.; Schajowicz, F. 1977. Metal carcinogenesis: a study of the carcinogenic activity of solid metal alloys in rats. J. Bone J. Surg. A59: 622-624.

Gennart, J. P.; Baleux, C.; Verellen-Dumoulin, Ch.; Buchet, J.P.; De Meyer, R.; Lauwerys, R. 1993. Increased chromatid exchanges and tumor markers in workers exposed to elemental chromium-, cobalt- and nickel-containing dusts. Mut. Res., 299: 55-61.

Gillespie, W.J.; Henry, D.A.; O'Connell, D.L.; Kendrick, S.; Juszczak, E.; McInnery, K.; Derby, L. 1996. Development of hematopoietic cancers after implantation of total joint replacement. Clin. Orthop. HD-329 Suppl: S290-296.

Gillespie, W.J.; Frampton, C.M.A.; Hendersen, R.J.; Ryan, P.M. 1988. The incidence of cancer following total hip replacement. J. Bone J. Surg. Br. 70: 539-542.

Griesemer, R.A.; Cueto, C. 1980. Toward a classification scheme for degrees of experimental evidence for the carcinogenicity of chemicals in animals. In: Molecular and Cellular Aspects of Carcinogen Screening Tests. IARC Scientific Publications, No. 27. 370 pp. Lyon, France: IARC, pp. 259-281.

Haber, L. T.; Erdreicht, L.; Diamond, G. L.; Maier, A. M.; Ratney, R.; Zhao, Q.; and Dourson, M. L. 2000 Hazard Identification and Dose Response of Inhaled Nickel-Soluble Salts. Regulatory Toxicology and Pharmacology, 31: 210-230.

Hagmar, L.; Bonassi, S.; Strömberg, U.; Brøgger, A.; Knudsen, L.; Norppa, H.; Reuterwall, C; and ESCH 1998. Chromosomal aberrations in lymphocytes predict human cancer: a report from the European study group pon cytogenetic biomarkers and health (ESCH). Can. Res. 58: 417-4121.

Haudrechy, P. Foussereau, J., Mantout, B. Baroux, B. 1994. Nickel release from nickel plated metals and stainless steels. Contact Derm., 31: 249-255.

Haudrechy, P. Pedarre, P. 1997. Test report of Ni release for various stainless stees in synthetic sweat. Ugine Savoie Centre de Recherches, (unpublished).

Hildebrand, H. F.; Ostapczuk, P.; Mercier, J. F.; Stoeppler, M.; Roumazeille, B.; Decoulx, J. 1988. Orthopedic implants and corrosion products: Ultrastructural and analytical studies of 65 patients. In Biocompatibility of Co-Cr-Ni alloys. Hildebrand, H. F.; Champy, M.; eds. London, United Kingdom. Plenum Publishing Corporation, p. 133-153.

Horn-Ross, P. L.; Ljung, B. M.; Morrow, M. 1997. Environmental factors and the risk of salivary gland cancer. Epidemiology, 8: 414-419. 1997

Hueper, W. C. 1958, Experimental studies in metal carcinogenesis: IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalation of powdered metallic nickel. AMA Arch. Pathol., 65: 600-607.

Hueper, W. C. and Payne, W. W. 1962. Experimental studies in metal carcinogenesis. Arch. Environ. Health, 5: 445-462.

Hueper, W. C 1955. Experimental studies in metal carcinogenesis. IX. Cancer produced by parenterally induced metallic nickel. J. Nat. Cancer Inst., 16: 55-73.

Kumar, R., Srivastava, P. K., Srivastava, S. P. 1994. Leaching of heavy metals(Cr, Fe and Ni) from stainless steel utensils and food materials. Bull. Environ Contam. Toxicol., 53: 259-266.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1990. Chromium, Nickel and Welding. Volume 49. IARC, Lyon, France.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1999.Surgical Implants and Other Foreign Bodies. Volume 74. IARC, Lyon, France.

ICNCM Report. 1990. Report of the International Committtee on Nickel Carcinogenesis in Man. Scand. J. Work Environ. Health 16(1): 1-82.

Ivankovic, S., Zeller, W. J, 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.

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.

Jasmin, G. and Riopelle, J. L.1979. Renal carcinomas and erythrocytosis in rats following intrarenal injection of nickel subsulfide. Lab. Invest., 35: 71-78.

Jelmert, O.; Hansteen, I.-L.; Langard, S. 1995. Cytogenetic studies of stainless steel welders using the tungsten inert gas and metal inert gas methods for welding. Mutat. Res.342: 77-85.

Knudsen, L. E.; Boisen, T.; Christensen, J. M.; Jelnes, J. E.; Jensen, G. E.; Jensen, J. C.; Lundgren, K.; Lundsteen, C.; Pedersen, B.; Wassermann, K.; Wilhardt, P.; Wulf, H. C.; Zebitz, U. 1992. Biomonitoring of genotoxic exposure among stainless steel welders. Mutat. Res. 279: 129-143.

Li, X. Q., Hom, D. L., Black, J., Stevenson, S. 1997. Relationship between metallic implants and cancer: a case-control study in a canine population. VCOT, 6: 70-74.

Mayer, C.; Klein, R. G.; Wesch, H.; Schmezer, P. 1998. Nickel subsulfide is genotoxic in vitro but show no mutagenic potential in respiratory tract tissues of BigBlue rats and Muta Mice in vivo after inhalation. Mutat. Res. 420:85-98.

McGregor, D. B., Baan, R. A., Partensky, C., Rice, J. M., Wilbourn, J. D. 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. of Cancer, 36: 307-313.

Memoli, V.A.; Urban, R.M.; Alroy, J.; Galante, J.O. 1986. Malignant neoplasms associated with orthopedic implant materials in rats. J. Orthop. Res., 4: 346-355.

Menné, T., Brandrup, F., Thestrup-Pedersen, K., Veien, N. K., Andersen, J. R., Yding, F, Valeur, G. 1987. Patch test reactivity to nickel alloys. Contact Dermatitis, 16: 255-259.

Mitchell, D.F.; Shankwalker, G.B.; Shazer, S. 1960. Determining the tumorigenicitiy of dental materials. J. Dent. Res. 39: 1023-1028.

Moffa, J. P. 1982. Biological effects of nickel-containing dental alloys. Council on dental Materials, Instruments and Equipment. J. Am. Dent. Assoc. 104: 501-505.

Moulin J.J., Portefaix, P., Wild, P., Mur, J. M, Smagghe, G., Mantout, B. 1990. Mortality study among workers producing ferroalloys and stainless steel in France. Br. J. Ind. Med., 47: 537-543.

Moulin J.J., Wild, P., Mantout, B., Fournier, Betz, M., Mur J. M, Smagghe G., Mur, J. M 1993. Mortality from lung cancer and cardiovascular diseases among stainless steel producing workers. Cancer Causes Control, 4: 75-81.

Moulin J.J., Clavel, T., Roy, D.; Danaché, B., Marquis, N., Févotte, J., Fontana, J. M. 2000. Risk of lung cancer in workers producing stainless steel and metallic alloys. Int. Arch Occup. Environ. Health, 73: 171-180.

Muhle, H., Bellman, B., Takenaka, S., Fuhst, R., Mohr, U., and Pott, F. 1992. Chronic effects of intratracheally instilled nickel-containing particles in hamsters. In: Nickel and Human Health: Current Perspectives. Nieboer, E.; Nriagu, N. O., eds. New York, NY: John Wiley & Sons, Inc. p. 467-479.

NTP (National Toxicology Program) Technical Report 1996. Toxicology and carcinogenesis studies of nickel subsulfide in F344/N rats and B6C3F$_1$ mice. NTP TR 453, NIH publication Series No. 96-3369.

Nyren, O.; McLaughlin, J.K.; Gridley, G.; Ekbom, A.; Johnell, O.; Fraumeni Jr., J.F.; Adami, H-O. 1995. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. JNCI, 87 (1): 28-33.

Oller, A. R., Costa, M., and Oberdörster, G. 1997. Carcinogenicity assessment of selected nickel compounds. Toxicol. Appl. Pharmacol., 143: 152-166.

Paavolainen, P.; Pukkala, E.; Pulkkinen, P.; Visuri, T. 1999. Cancer incidence in Finnish hip replacement patients from 1980 to 1995: a nationwide cohort study involving 31,651 patients. J. Arthroplasty, 14 (3): 272-280.

Paton, G. R. Allison, A. C. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16: 332-336.

Pauli, B.M.; Urban, R.M.; Galante, J.O. 1986. Carcinogenic evaluation of porous sintered powder composites. Trans. Orthop. Res. Soc., 11: 102.

Popp, W.; Vahrenholz, C.; Schmieding, W.; Krewet, E.; Norpoth, K. 1991. Investigations of the frequency of DNA strand breakage and cross-linking and of sister chromatid exchange in the lymphocytes of electric welders exposed to chromium- and nickel-containing fumes. Int. Arch. Occup. Environ. Health, 63: 115-120.

Pott, F., Rippe, R. M., 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.

Pott, F., Ziem, U., Reiffer, F. J., Huth, F. Ernst, H., and Mohr, U. 1987. Carcinogenicity studies on fibers, metal compounds, and some other dusts in rats. Exp. Pathol., 32: 129-152.

Rigaut, J. P. 1983. Rapport Preparatoire sur les Criteres de Sante pour le Nickel (Preparatory Report on Health Criteria for Nickel). Doc. CCE/Lux/V/E/24/83, Luxemburg Commission of the European Communities.

Senft, V., Losan, F., Tucek, M. (1992), Cytogenetic analysis of chromosomal aberrations of peripheral lymphocytes in workers occupationally exposed to nickel. Mutat. Res., 279, 171-179.

Sharkness, C.M.; Acosta, S.K.; Moore, R.M.; Hamburger, S.; Gross, T.P. 1993. Metallic implants and their possible association with cancer. J. Long-Term Effects Med. Impl., 3 (3): 237-249.

Sunderman, F.W., Jr. 1989. Carcinogenicity of metal alloys in orthopedic prostheses: clinical and experimental studies. Fundam. Appl. Toxicol., 13: 205-216.

Sunderman, F. W.; McCully, K.; Hopfer, S. M. 1984. Association between erythrocytosis and renal cancers in rats following intrarenal injection of nickel compounds. Carcinogenesis, 5: 1511-1517.

Sunderman, F. W., Jr. 1984. Carcinogenicity of nickel compounds in animals. In: Sunderman, F. W., Jr., ed. Nickel in the human environment (IARC scientific publication No. 53). Lyon, France: International Agency for Research on Cancer; pp. 127-142.

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.

Takamura, K., Hayashi, K., Ishinishi, N., Yamada, T., Sugioka, Y. 1994. Evaluation of carcinogenicity and chronic toxicity associated with orthopedic implants in mice. J. Biomed Mater Res., 28: 583-89.

Török, L., Greczy, I., Ocsai, H. Czako J. 1995. Investigation into the development of allergy to metal in recipients of implanted prostheses: a prospective study. Eur. J. Dermatol., 5: 294-295.

Waalkes, M.P.; Rehn, S.; Kasprzak, K.S.; Issaq, H.J. 1987. Inflammatory, proliferative, and neoplastic lesions at the site of metallic identification ear tags in Wister [Crl: (WI)BR] rats. Cancer Res., 47: 2445-2450.

Waksvik, H., Boysen, M. 1982. Cytogenetic analyses of lymphocytes from workers in a nickel refinery. Mutat. Res., 103, 185-190.

Waksvik, H., Boysen, M., Høgetveit, A. 1984, Chromosome aberrations and sister-chromatid exchanges in retired nickel refinery workers. Mutat. Res., 130, 250-251.

Werfel, U.; Langen, V.; Eickhoff, I.; Schoonbrood, J.; Vahrenholz, C.; Brauksiepe, A.; Popp, W.; Norpoth, K. 1998. Elevated DNA single strand breakage frequencies in lymphocytes of welders exposed to chromium and nickel. Carcinogenesis, 19: 413-418.

Wortley, P.; Vaughan, T. L.; Davis, S.; Morgan, M. S.; Thomas, D. B. 1992. A case-control study of occupational risk factors for laryngeal cancer. Br. J. Ind. Med. 49: 837-44.