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Via Overnight Mail
Dr. Mary S. Wolfe
Executive Secretary
National Toxicology Program
111 T.W. Alexander Drive
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Re: *10th Report on Carcinogens* Listing Recommendation for Metallic Nickel and Nickel Alloys

Dear Dr. Wolfe:

On behalf of the Specialty Steel Industry of North America ("SSINA"), we submit the following comments regarding the proposed listing of "metallic nickel and certain nickel alloys" in the *10th Report on Carcinogens* ("*RoC*") by the National Toxicology Program ("NTP"). 65 Fed. Reg. 61,352 (Oct. 17, 2000). SSINA strongly objects to the listing of "metallic nickel and certain nickel alloys" as "reasonably anticipated to be human carcinogens" as recommended in the *Draft Report on Carcinogens Background Document for Metallic Nickel and Certain Nickel Alloys* ("*Background Document*"). Such a listing would totally abdicate the application of sound scientific judgment in reviewing the available toxicological and epidemiological data, and ignore over 100 years of actual human experience using metallic nickel and nickel alloys with no significant adverse effects on human health.

I. BACKGROUND

SSINA is a national trade association comprised of 15 producers of specialty steel products, including stainless, electric, tool, magnetic, and other alloy steels. SSINA members account for over 90 percent of the specialty steel manufactured in the United States, and represent the largest consumers and users of nickel in the United States. As nickel is a significant alloying agent in the production of many stainless steels and other high performance alloys, SSINA members are interested in the proper characterization of this metal for potential regulatory purposes. In particular, SSINA is very concerned about the potential listing of metallic nickel and nickel alloys in the *Report on Carcinogens*, given that the available evidence demonstrates that nickel metal and alloys are safe and valuable materials and are not associated with increased incidences of carcinogenicity.

Specialty steels play an important and expanding role in the U.S. economy and touch our daily lives in a wide range of uses. They have been used safely for over 100 years and are essential in today's industrialized economy, serving critical national defense needs and applications in aerospace; aircraft; automobiles; appliances; communications, electronic, marine, and power-generating equipment; home utensils and cutlery; construction products; food and chemical processing plant equipment; and medical, health, and sports equipment. Specialty steels are valued for these uses due to their exceptional hardness, strength, and resistance to heat, corrosion and abrasion.

As detailed in these comments, SSINA adamantly objects to the recommended listing of nickel metal and certain nickel alloys as "reasonably anticipated" human carcinogens for the following reasons:

(1) Associating metallic nickel and certain nickel alloys with cancer ignores over a century of human experience using nickel and nickel alloys safely;

(2) The conclusions in the *Background Document* regarding metallic nickel and certain nickel alloys fail to reflect the application of sound scientific judgment, particularly considering that the alleged evidence of carcinogenicity in laboratory animals is associated with forms of the metal/alloys (powder) and routes of exposure that are not relevant to humans;

(3) The data cited with respect to prosthetic implants comprised of nickel alloys does not support listing; and

(4) Given the unique properties possessed by individual alloys, NTP should not broadly classify all nickel alloys in the same listing, but separately review each alloy.

Listing metallic nickel and nickel alloys as "reasonably anticipated" human carcinogens would ignore the fact that nickel alloys such as stainless steel have been used for several decades and are universally recognized as being safe for use in a wide variety of consumer products, including cookware, eating utensils, kitchen and restaurant equipment, surgical implants, *etc.* Any classification of these benign nickel alloys as carcinogens would be entirely improper. The impact of such a gross misclassification upon the stainless steel industry could be devastating.

With respect to stainless steel in particular, NTP should acknowledge that the available data provide no indication that stainless steel is associated with carcinogenicity. Significantly, to address whatever data gaps may exist, the International Stainless Steel Federation ("ISSF") has recently initiated a comprehensive carcinogenicity study of the various types of stainless steel. The results of this study will be available in a couple of years. The Nickel Producers Environmental Research

Association ("NiPERA") is conducting a series of cancer studies on various nickel compounds, metallic nickel, and nickel alloys. The ISSF and NiPERA studies will provide definitive evidence on the carcinogenicity potential of nickel metal, compounds, and alloys, including stainless steel. Accordingly, NTP should consider deferring its listing review until the results of these studies can be obtained.

II. HUMAN EXPERIENCE INDICATES THAT NICKEL METAL AND ALLOYS POSE NO SIGNIFICANT RISKS TO HEALTH

NTP recognizes that metallic nickel and nickel alloys have been "[w]idely used in commercial applications for over 100 years." 65 Fed. Reg. at 61,354. Despite this heavy usage of nickel, the *Background Document* acknowledges that there is no sufficient evidence from humans associating nickel metal and nickel alloys with cancer. *Background Document* at 33-36. Similarly, the International Agency for Research on Cancer ("IARC") found "inadequate evidence of carcinogenicity in humans" for nickel metal and alloys, as well as metallic implants. *Id.* at 33, 35.

Given the widespread usage of nickel metal and alloys in society, if nickel metal and alloys were truly associated with an increased cancer risk, one would expect to find significant statistical evidence of carcinogenicity associated with these substances in humans. The lack of any such evidence indicates that no significant risk exists. NTP should consider this extensive human experience with nickel metal and alloys when reviewing the listing recommendation.

III. APPLYING SOUND SCIENTIFIC JUDGMENT TO THE AVAILABLE EVIDENCE COMPELS THE CONCLUSION THAT NO LISTING IS WARRANTED

NTP's listing criteria incorporate the overriding principle that "[c]onclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information." NTP, *9th Report on Carcinogens* at I-2 (2000). Such relevant information includes "route of exposure." *Id.* NTP also notes that a substance is not reasonably considered to be carcinogenic in humans, despite evidence of carcinogenicity from laboratory animals, if data indicate that "the agent acts through mechanisms which do not operate in humans." *Id.* Based on the *Background Document*, however, it does not appear that NTP has applied these principles when drawing conclusions from the animal data available for nickel metal and alloys.

Humans are exposed to nickel through inhalation, ingestion, and skin contact. *Background Document* at 15. These routes of exposure, therefore, are the only meaningful exposure routes when

assessing the probity of animal studies for classifying the carcinogenic potential of nickel metal and alloys.[1]

Consistent with human experience, the *Background Document* presents no animal studies that reliably associate nickel metal or alloys with cancer via the inhalation,[2] ingestion, or dermal contact routes of exposure. *See Background Document* at 37-51. Aside from inhalation, the cited studies involve intratracheal instillation and intravenous, intramuscular, intrapleural, subcutaneous, intraperitoneal, intrarenal, subperiosteal, and intramedullary injection -- none of which are relevant routes of exposure for humans. *See id.* Further, with respect to nickel alloys, the injections involved nickel alloy powders, which is not a realistic exposure pattern for humans. *Id.* at 43. Humans are only likely to be exposed to massive forms of nickel alloys, and then only via dermal contact.[3] Moreover, as discussed in Sharkness *et al.* (1993), tumorigenic responses may be due to persistent tissue irritation and inflammation caused by the mere implantation of a foreign body, regardless of the composition of the implant.

The comments submitted by NiPERA provide a thorough examination of the available human and animal data cited in the *Background Document,* and are hereby incorporated into these comments. In summary, the NiPERA comments demonstrate that:

- Data from humans show no causal relationship between exposure to metallic nickel or nickel alloys and increased incidences of cancer;

- The only animal studies that show evidence of tumorigenic responses involve routes of exposure that are not relevant to humans, and often involve animals that experienced high toxicity during the study;

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[1] Some nickel alloys also are a primary component of certain medical implants. *Id.* at 16. Only for these specific alloys would animal implantation studies be meaningful. The data cited in the *Background Document* regarding medical implants are discussed in the next section of these comments.

[2] The one cited inhalation study that indicated a tumorigenic response via inhalation (Hueper 1958) involved extraordinarily high levels of nickel (15 mg/m^3 administered for six hours per day for four or five days per week over 21 months) and resulted in high mortality rates among the subject guinea pigs. In contrast, the three other cited studies revealed no tumorigenic responses.

[3] Nickel alloy powders will not be present in drinking water, and metal ions that may be released at low levels during cooking with stainless steel pots and pans do not represent exposure to the nickel alloy itself.

- There is no evidence of carcinogenicity from human or animal studies involving exposure to metallic nickel or nickel alloys via inhalation, ingestion, or dermal contact -- the only relevant routes of exposure for humans; and

- Mechanistically, nickel metal is unlikely to be an effective respiratory cancer initiator.

Accordingly, applying sound scientific judgment and considering all the relevant factors, especially route of exposure, there is no basis for listing nickel metal and alloys as "reasonably anticipated to be human carcinogens."

IV. EVIDENCE PERTAINING TO MEDICAL IMPLANTS DOES NOT SUPPORT THE LISTING OF NICKEL METAL AND ALLOYS

Nickel alloy medical implants have been widely used in the United States for decades without accompanying reports of significant adverse effects. In 1988, over 6.5 million metallic orthopedic implants were in use in the United States (Sharkness *et al.,* 1993) -- a number that most likely is larger today -- but only 35 cases of tumors in the region of the implant had been reported over the past 30 to 40 years (McGregor *et al.,* 2000).[4]

A. Common Nickel Alloy Medical Implants In Use Today Are Biocompatible And Not Associated With Increased Cancer Risk

Numerous studies have established the biocompatability of nickel alloy implants that are in use today. For example, nickel-titanium implants (which contains 55 percent nickel by weight) have been the subject of numerous biocompatability studies. *See* Attachment A.[5] These studies have uniformly found that nickel-titanium is highly biocompatible; none have found any indication of cancer risk. In fact, nickel-titanium has been used safely in humans since at least the 1970s as the primary material in suture anchors, staples, stents, blood filters, vascular grafts, orthodontic appliances, and other medical devices.

The lack of cancer risk associated with nickel-titanium alloys stands in stark contrast to the extraordinary statement in the *Background Document* that "[i]n general, alloys containing > 50%

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[4] Further, as explained below, a number of factors other than the metallic content of the implants likely contributed to such tumors.

[5] Attachment A contains a bibliography and several papers regarding studies on the biocompatability of nickel-titanium alloys.

nickel were carcinogenic in [animal] implantation studies." *Background Document* at 51. Nickel-titanium alloys demonstrate that high nickel content alloys are not necessarily (if at all) carcinogenic, and that any generic classification of such alloys is scientifically unsound. Further, the *Background Document* presents no data suggesting that nickel-titanium alloys are associated with increased cancer risks. To SSINA's knowledge, other than nickel-titanium, no other high nickel content (greater than 50 percent nickel) alloys are used as implants in the United States today.

Accordingly, given that the available data on nickel-titanium alloys show no increased cancer risk and no other medical implants comprised of high nickel content alloys are known to be in use in the United States today, it would be legally and scientifically improper for NTP to list either nickel alloy medical implants or high nickel content alloys generally as reasonably anticipated human carcinogens. If NTP is to make a listing, it must identify specific nickel alloys or medical implants that have demonstrated evidence of tumorigenic activity. SSINA does not believe that sufficient evidence exists to proceed with such a listing.

B. Data From Human And Animal Studies Do Not Support A Finding That Nickel Alloy Implants Are Carcinogenic

The majority of studies cited in the *Background Document* show no evidence of a carcinogenic effect for nickel alloy medical implants. *See id.* at 35-36. As a result, the *Background Document* concludes that these studies "generally suggest that there is little excess risk associated with orthopedic implants." *Id.* at 36.[6]

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[6] While the *Background Document* suggests that these studies may underestimate the risk of cancer, the reasons cited for the possible underestimation of cancer risk from metallic implant studies are flawed in a number of ways, including:

(1) As discussed below, many of the existing studies included patients with rheumatoid arthritis, which is a risk factor for lymphohematopoietic cancer. *Id.* at 36. Such patients can not reasonably be associated with a "healthy patient" effect that serves to understate the possible cancer risk for the general population.

(2) Decades of human experience suggests that the most obvious explanation for the lack of cancer findings is that cancer was in fact not a significant risk, and not because "some cohorts had few cases for some sites of interest" or some studies involved follow-up periods that were potentially too short to identify cancers with long latencies.

(continued...)

The studies that associate nickel alloy implants with increased incidences of carcinogenicity do not support the conclusion that the nickel alloy -- or release of nickel ions from the nickel alloy -- is the causative tumorigenic agent. A number of confounding factors make such a conclusion unreliable:

- Most of the studies that found lymphohematopoietic cancers included patients with rheumatoid arthritis, which the *Background Document* (at 36) acknowledges is a risk factor for this type of cancer. Accordingly, NTP concluded that "inclusion of these patients in other cohorts could create the appearance of an association of implants with lymphohematopoietic cancers in the absence of a true effect." *Id.* at 36.

- The studies involving lymphohematopoietic cancer studies also failed to provide information on the use of immunosuppressive therapy in the subjects.

- Only one study (Visuri *et al.* 1996) examined metal-on-metal implants (which have not been used in the U.S. since the 1970s) in comparison to metal-on-polyethylene implants, with increased cancer risk being confined to the former group. *Id.* Metal-on-metal implants are recognized to result in the release of more metal debris due to increased abrasion, which also could trigger a greater inflammatory response.

- Tumorigenic responses may be due to non-specific local responses to implanted foreign material. As noted in Sharkness *et al.* (1993), persistent tissue irritation and inflammation by the foreign body can lead to tumor formation at the implant site.

After reviewing available data from animal studies, in 1999 IARC concluded that there was "inadequate evidence" regarding the carcinogenicity of nickel alloy implants. The *Background Document* fails to acknowledge this conclusion in reviewing the implant data, and ignores a number of significant factors concerning these animal studies, including:

- Tissue irritation may explain the increased incidence of tumor formation at the site of ferronickel alloy ear tags in Waalkes *et al.* (1987). *Background Document* at 45. The Waalkes study also was focused on assessing the carcinogenicity of cadmium chloride, not nickel alloys, and, hence, is of limited value. *See id.* Similarly, the cancers identified in Buhr *et al.* (1990) were intentionally induced by 1,2-

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[6] (...continued)

(3) The few incidences in which tumors were found to develop in implantation studies very likely resulted from inflammatory responses associated with the introduction of foreign material into the body, particularly metal-on-metal implants (which are no longer in use) that are plagued by excessive abrasion.

dimethylhydrazine, and the results, at best, show that the ferronickel alloy staples may have promoted -- but not initiated -- tumor development. *See id.* at 46.

- As detailed in the comments submitted by NiPERA, as the *Background Document* (at 47-48) fails to recognize, the study by Memoli *et al.* (1986) only identified tumorigenic responses in animals implanted with certain powdered and pelletized nickel alloys. These implant forms are not relevant to potential human exposures. In contrast, the Memoli study found that the implantation of various stainless steel and nickel alloy rods did not exhibit such tumors. Further, the influence of inflammation on the observed tumor responses was not addressed. The Memoli study also noted that the intramedullary implantation site may have played a role in the observed tumorigenic response.

- Similar to the Memoli study, the study by Mitchell *et al.* (1960) involved the administration of nickel-gallium pellets to rats. Pelletized implants, like powders, are not relevant to potential human exposures to implants.

- In Takamura *et al.* (1994), the experimental animals implanted with a 96 percent nickel content alloy rod experienced very high (87 percent) mortality.

When the available evidence is combined with general human experience, it should be clear that nickel alloy implants are not properly associated with increased cancer risks. Further, given the widespread usage of nickel alloy implants, which involve intimate human contact with nickel alloys and in some cases nickel metal released from the alloy, the available evidence indicates that nickel metal and alloys pose no significant cancer risk and should not be listed as "reasonably anticipated" human carcinogens. Any conclusion that would associate nickel alloys with increased cancer risk would be legally and scientifically unsupportable.

V. EACH ALLOY IS A UNIQUE SUBSTANCE AND SHOULD BE SEPARATELY REVIEWED

An alloy is a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. Alloys are not simply mixtures in which the constituents retain their separate identities and can easily be separated. During manufacture the constituents are heated to very high temperatures, usually above their melting points. The constituents then react with, and dissolve into, each other to form alloys consisting of new crystalline structures and compounds with new properties that are retained during cooling to room temperature. The original elemental constituents can not be separated from each other by normal physical means.

As a result, the physical, chemical, and toxicological properties of an alloy are different from those of its elemental constituents. Accordingly, the carcinogenic potential of nickel alloys must be evaluated separately from that of metallic nickel. And, because of the unique properties that each alloy possesses -- which are influenced by a number of factors, including its chemical composition, history of melting and heat treatment, and any mechanical working to which it was subjected -- judgments regarding the carcinogenic potential of an alloy can not be made on the basis of the concentration of nickel or any other metal in the alloy.

Of particular significance in assessing cancer risk, the unique properties of each individual alloy affect the release rate and bioavailability of individual metal ions. Alloys that are more corrosion resistant, such as stainless steels and nickel-titanium, are expected to present lower biological risks.[7]

In sum, because each alloy is essentially a separate substance with separate properties, NTP can not issue a generic listing of "nickel alloys." Rather, the agency must separately consider each alloy. As noted above with respect to nickel-titanium (a 55 percent nickel alloy), a generic listing of alloys that contain in excess of a certain level of nickel would be wholly inappropriate and legally and scientifically flawed.

VI. NTP SHOULD ACKNOWLEDGE THAT STAINLESS STEEL IS NOT ASSOCIATED WITH AN INCREASED RISK OF CANCER

SSINA believes that a reasonable evaluation of the available evidence demonstrates, as explained in the foregoing comments, that there is no basis to list metallic nickel or any nickel alloy as a reasonably anticipated human carcinogen. Even the evidence presented in the flawed *Background Document* makes clear that, at most, only *certain* nickel alloys, specifically some alloys with nickel content in excess of 50 percent, may be associated with increased risks of cancer. *See Background Document* at 51. Because stainless steels do not contain nickel at such levels -- the

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[7] A thorough examination of alloys and the factors that contribute to their potential carcinogenicity is contained in the comments of NiPERA, which are hereby incorporated by reference.

Corrosion resistance in stainless steels is provided by a passive surface film which acts as a barrier between the alloy and the surrounding medium. The passive film is a continuous, non-porous, and insoluble film which, if broken under normal conditions, is self-healing. While chromium plays the most important role in forming the passive film for stainless steel, nickel plays a role in promoting repassivation.

maximum nickel content of any type of stainless steel is 38 percent -- NTP should make clear in its evaluation that stainless steel is not associated with an increased risk of cancer.

VII. THE *BACKGROUND DOCUMENT* MISCHARACTERIZES THE RESULTS OF A STUDY OF FEMALE HIGH NICKEL ALLOY WORKERS

The *Background Document* egregiously mischaracterizes the findings presented in a study (Arena *et al.* 1999) of 2,877 female workers in the high nickel alloy production and fabrication industry. *See Background Document* at 34. The *Background Document* states that this study found that the "[r]isk of lung cancer was elevated." *Id.* However, the authors explicitly state that the risks for all cancers, lung cancer, and breast cancer "were nonsignificant when mortality was compared to the US female population." Arena *et al.*, *Issues and Findings in the Evaluation of Occupational Risk Among Women High Nickel Alloy Workers*, 36 Amer. J. Ind. Med. 114 (1999) (Attachment B). Further, "[n]o relationship between mortality and length of time employed in the industry or work area was identified." *Id.*

The female high nickel alloy worker study was taken from a larger study of 31,000 high nickel alloy workers, who were likely exposed to nickel in metallic and/or oxidized forms. The results of the study were discussed in the October 1998 issue of the *Journal of Occupational and Environmental Health (*Arena *et al., Using Alternative Comparison Populations to Assess Occupation-Related Mortality Risks*)(Attachment B). The broader study found that nickel alloys are produced without subjecting workers to increased mortality risks.

The mischaracterization of the Arena study raises questions about the general accuracy and objectivity of the *Background Document*. Interpreting study results, especially when numerous confounding factors may be present, is not a simple process, as the authors of the Arena study made clear with respect to the use of proper comparison populations. NTP should use great care in evaluating the studies cited to support supposed claims that a substance is associated with increased cancer risk. Such care was not exercised with respect to the Arena study and perhaps, as with the IARC listing discussed below, more broadly throughout the *Background Document*.

VIII. THE *BACKGROUND DOCUMENT* ERRONEOUSLY IDENTIFIES THE IARC LISTING FOR METALLIC NICKEL

The *Background Document* states that IARC lists "nickel and nickel compounds" as "*carcinogenic to humans* (Group 1)." *Background Document* at 1. In fact, this is not true. In 1990 IARC listed metallic nickel as "possibly carcinogenic to humans" (Group 2B). This listing decision was based on the finding, from very limited information, that there was "sufficient evidence" in experimental animals for the carcinogenicity of metallic nickel. Today, however, as detailed in the comments submitted by NiPERA, in light of new scientific developments it is highly unlikely that IARC would reach this same conclusion and list metallic nickel even as a "possible" carcinogen.

IARC also found that there was "inadequate evidence in humans" and "limited evidence in experimental animals" for the carcinogenicity of nickel alloys. Such findings correlate to a Group 3 "not classifiable as to its carcinogenicity to humans" IARC classification.

Nevertheless, the recommendation in the *Background Document* attempts to go further than the current IARC "possibly carcinogenic" listing and identify metallic nickel and nickel alloys as "reasonably anticipated" human carcinogens. An objective review of the available evidence should make clear that this recommendation is unreasonable. NTP appears to be going well beyond the conclusions reached by others and ignoring more current and compelling information to the contrary.

IX. CONCLUSION

Based on the foregoing comments, SSINA strongly believes that the recommendation in the *Background Document* to list metallic nickel and nickel alloys as "reasonably anticipated" human carcinogens is unsupported by the available evidence, contrary to sound scientific judgment, and at odds with decades of safe human experience with these materials. In particular:

(1) The animal evidence relied on to support the recommendation involves tumor formation by routes of exposure that are not relevant to and totally inappropriate for humans;

(2) The *Background Document* fails to recognize that each nickel alloy has specific physical, chemical, and toxicological properties that affect potential carcinogenicity (such as the passivation qualities of stainless steels). Sound science dictates that the agency separately evaluate each alloy, rather than issuing a generic listing such as "certain nickel alloys";

(3) The evidence regarding nickel alloy medical implants neither supports the listing of metallic nickel and nickel alloys nor demonstrates that such alloys are associated with significant cancer risks; and

(4) The few effects that are shown in the cited studies are reasonably attributable to confounding factors, such as rheumatoid arthritis, non-specific inflammatory responses, increased irritation and corrosion by metal-on-metal implants, *etc.*

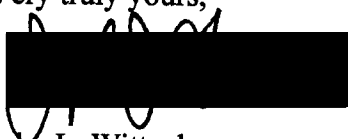
The evidence is clear that metallic nickel and nickel alloys, especially stainless steels, do not pose a cancer risk to humans. Any conclusion that would associate metallic nickel and nickel alloys with increased cancer risk would be legally and scientifically unsupportable. Further, a generic listing of alloys containing nickel above a certain level (*e.g.*, 50 percent) would be wholly inappropriate,

given that each alloy is, in essence, a unique substance with unique properties (*e.g.*, corrosion-resistance) that influence carcinogenic potential.

NTP decisions have significant downstream regulatory and economic impacts. Moreover, identification as a carcinogen by NTP -- or other agency classification decisions based on NTP conclusions -- has widespread social and economic impacts (*e.g.*, toxic tort litigation, consumer product deselection). Accordingly, NTP has a legal duty to ensure that its decisions are based on sound science and the product of reasoned decision making before stigmatizing a substance as a known or reasonably anticipated carcinogen. The available evidence for metallic nickel and nickel alloys in particular does not meet this standard.

If you have any questions or we may be of any further assistance, please do not hesitate to contact us.

Very truly yours,



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Attachments

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