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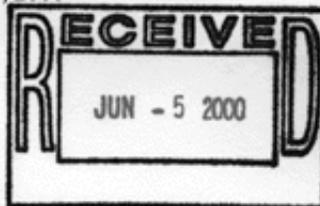
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June 1, 2000



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

Re: 10th Report on Carcinogens, 65 Fed. Reg. 17889 (April 5, 2000)

Dear Dr. Jameson:

I am enclosing the Comments of the Nickel Development Institute and Inco United States, Inc. in response to the NTP's request for information relating to the potential listing of Metallic Nickel and Nickel Alloys in the 10th Report on Carcinogens (RoC). Also enclosed is a copy of this cover letter and a stamped, self-addressed envelope. Please sign or stamp the copy of the cover letter to acknowledge receipt of these Comments, and mail it back to me.

While Metallic Nickel and Nickel Alloys are the focus of NTP's request for information in the April 5 Federal Register notice, we understand that further consideration will be given to the potential listing of Nickel Compounds in the 10th RoC as well. Although various groups commented on the proposed classification of Nickel Compounds during the 9th RoC listing cycle in 1998, the listing decision for Nickel Compounds was deferred until the 10th RoC. Additional information relevant to evaluating Nickel Compounds for potential listing in the RoC has become available since RG1, RG2, and the Board of Scientific Counselors Subcommittee considered this issue two years ago. Accordingly, we expect that nickel producers and nickel users will want to submit further comments on the proposed listing of Nickel Compounds, as deliberations on the 10th RoC proceed.

If you have any questions regarding the enclosed Comments or the attached Appendices, please let me know.

Very truly yours,

Neil J. King

Enclosures

BEFORE THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM

Substances, Mixtures and Exposure
Circumstances Proposed for Listing
In the Report on Carcinogens,
Tenth Edition, 66 Fed. Reg. 17889
(April 5, 2000)

COMMENTS OF
THE NICKEL DEVELOPMENT INSTITUTE
and
INCO UNITED STATES, INC.

Communications Regarding These
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June 1, 2000

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Introduction

In the Federal Register of April 5, 2000, the National Toxicology Program (NTP) announced its intention to review 11 substances, mixtures, and exposure circumstances for possible listing in the 10th Report on Carcinogens (10th RoC). See 66 Fed. Reg. 17889. The notice solicits public input and relevant information regarding the potential carcinogenicity of the substances under consideration for listing, as well as production data, use patterns, or human exposure information. In addition, NTP has invited interested parties to identify scientific issues related to the listing of a specific nomination that should be addressed during the review process.

The present Comments are submitted by the Nickel Development Institute (NiDI) and Inco United States, Inc. (Inco). NiDI is an organization of the world's primary nickel producers. Inco's parent company, Inco Limited, a Canadian corporation, is a member of NiDI. We are responding to the Federal Register notice because "Nickel and Nickel Compounds including Metallic Nickel & Nickel Alloys" are among the nominations for possible listing in the 10th RoC.¹ The information provided in these Comments focuses on production data, use patterns, and occupational exposure. This information is presented largely in the form of Appendices to Part I of the Comments. A separate set of Comments—submitted by the Nickel Producers Environmental Research Association (NiPERA)—provides information regarding the potential carcinogenicity of Metallic

¹ The categories for which the nickel-related listings are being considered were not specified in the notice, and we understand that decisions regarding the listing categories have not yet been made.

Nickel and Nickel Alloys. NiDI and Inco have reviewed NiPERA's Comments on that issue and agree with the points set forth therein.

While Metallic Nickel and Nickel Alloys may be the focus of attention during the 10th RoC listing process, we understand that further consideration will be given to Nickel Compounds as well. Nickel Compounds were considered for listing as "*Known to be a Human Carcinogen*" in the 9th RoC, but the listing decision was deferred until the 10th RoC, so that Nickel Metal, Nickel Alloys and the various Nickel Compounds could be addressed at one time. We believe the decision to defer the listing determination for Nickel Compounds was sound, particularly since new information and evaluations relating to the potential carcinogenicity of various nickel compounds have become available since Nickel Compounds were considered for listing by RG1 and RG2 and by the Board of Scientific Counselors RoC Subcommittee in 1998. Accordingly, we expect that nickel producers and users will have more to say about the potential listing of Nickel Compounds as the 10th RoC listing process moves forward. In particular, we look forward to addressing any key scientific issues related to the listing proposals for Nickel Metal, Nickel Alloys, and Nickel Compounds when those issues are identified by NTP pursuant to the new listing procedures.² Part II of these Comments suggests several such issues that NTP may wish to highlight in its forthcoming notifications.

I. Production, Use, and Exposure Information

Some information regarding occupational and general population exposures to metallic nickel and nickel alloys is provided in NiPERA's Comments. As indicated by

² See NTP's Response to Public Comments and Discussion on the Preparation and Review of the *Report on Carcinogens*, pp. 2-3.

NiPERA, the principal way in which U.S. residents are exposed to metallic nickel and nickel alloys is through dermal contact. The general population has essentially no exposure to metallic nickel or nickel alloys through inhalation. Inhalation exposures to metallic nickel and nickel alloys in the occupational setting also are extremely limited. Similarly, metallic nickel and nickel alloys—as opposed to soluble nickel compounds—will not be present in drinking water or food, so there is no exposure to metallic nickel or nickel alloys via ingestion.³ The special considerations involving exposure to nickel alloys in prosthetic implants and dental appliances are discussed in NiPERA's Comments.

To help fill in the picture of production, use, and exposure circumstances, we are providing the following information in four Appendices to these Comments.

Appendix 1 is a compendium of nickel production and use information compiled by M.O. Pearce of NiDI for the Proceedings of the Nickel-Cobalt 97 International Symposium. Mr. Pearce's paper shows both the primary distribution and end-use distribution of nickel.

Appendix 2 is Chapter 4 of Volume II of the December 1996 *Occupational Exposure Limits Criteria Document for Nickel and Nickel Compounds* that was prepared for the European Commission's Directorate General V (the "DG-V Criteria Document"). This Chapter presents information on the occurrence, production, and use of nickel. Since it is focused on the European Union, the Chapter contains some information that is not relevant in the U.S. context—notably, information on primary nickel production,

³ As noted in NiPERA's Comments, while there may be some release of nickel ions (as opposed to nickel alloy material) into food from stainless steel cookware, the relative contribution of nickel to the diet from this source is quite small.

which occurs in several European countries but not in the United States. Much of the information presented on nickel-using industries, however, is relevant to the U.S.

Appendix 3 is Chapter 6 of Volume II of the DG-V Criteria Document. This Chapter presents occupational exposure information for various nickel-producing and nickel-using operations.

Appendix 4 is a copy of the August 1999 issue of *Nickel Magazine*. This special issue describes various uses of nickel that help protect the environment and play an important role in efforts to achieve sustainable development.

In addition to the foregoing, NTP should be aware that in the coming months, EPA will be releasing various components of the first National Air Toxics Screening Level Assessment as part of its Urban Air Toxics Program. Nickel compounds—though not metallic nickel—are among the substances to be included in the Assessment, which, *inter alia*, will present modeled ambient air data and population exposure estimates.

II. Scientific Issues That Need To Be Considered in Evaluating Nickel Metal, Nickel Alloys, and Nickel Compounds for Possible Listing in the 10th RoC

The following are among the significant scientific issues that need to be considered in determining whether nickel metal, nickel alloys, and/or the various types of nickel compounds should be listed in the 10th RoC—and, if so, in which category.

1. Different nickel species have different physicochemical characteristics that affect the bioavailability of the Ni²⁺ ion in different environmental and biological media and the ability of the Ni²⁺ ion to become available at a relevant biological site, such as the nucleus of an epithelial cell.
2. Different nickel species exhibit different toxicological properties in epidemiological and animal studies and in *in vitro* tests.

3. Each type of nickel alloy is a unique substance with its own special physicochemical and biological properties that differ from those of its individual metal constituents. The potential carcinogenicity of the principal categories of nickel alloys must, therefore, be evaluated separately from the potential carcinogenicity of nickel metal itself.
4. The most likely mechanism of nickel-related respiratory carcinogenicity suggests that some nickel species (*i.e.*, nickel subsulfide and, to a lesser extent, certain forms of oxidic nickel) are far more likely to be respiratory carcinogens than other forms of nickel (*i.e.*, metallic nickel, nickel alloys, and water soluble nickel compounds).
5. Animal evidence and mechanistic considerations indicate that soluble nickel compounds are more likely to have played an enhancing role, rather than acting as direct carcinogens, in epidemiological studies where an increased risk of respiratory cancer was found in certain cohorts within the nickel-producing industry.
6. Most epidemiological studies of workers in the nickel-producing and nickel-using industries are characterized by confounding exposures to a variety of nickel species and/or to other agents that are known to be respiratory carcinogens. In the 9th RoC, for example, NTP itself recently identified one such agent, *Strong Inorganic Acid Mists Containing Sulfuric Acid*, as a "Known Human Carcinogen." (This issue is of relevance mainly for evaluating the potential carcinogenicity of the various nickel compounds, since epidemiological studies have produced no evidence suggesting a causal association between exposure to metallic nickel or nickel alloys and increased respiratory cancer risk.)
7. The routes by which persons residing in the United States are exposed to nickel metal, nickel alloys, and the various nickel compounds differ. For water soluble nickel compounds, the principal routes of exposure will be inhalation and ingestion—with ingestion being far and away the primary source of exposure for the general population. For oxidic forms of nickel, inhalation will be the principal route of exposure. Exposure to sulfidic forms of nickel in the United States is negligible; to the extent it occurs, those exposures are through inhalation. By contrast, for the vast majority of the U.S. population, dermal contact is the only significant route of human exposure to metallic nickel—which is not present in food or drinking water and constitutes a negligible portion of the nickel present in ambient air. Even in occupational contexts, inhalation exposure to metallic nickel is minimal, with certain exceptions (notably, nickel powder metallurgy operations and, to a lesser extent, nickel-battery manufacturing and catalyst production). Dermal contact also is the principal route of exposure to nickel alloys, supplemented in special cases by exposure through prosthetic implants and dental appliances.
8. The points outlined in paragraph 7 above are particularly important because nickel-related carcinogenicity appears to be route-specific, as well as species-

specific. Thus, a nickel species that is tumorigenic via one route of exposure (*e.g.*, injection) should not be presumed to present a carcinogenic risk via other routes of exposure. Accordingly, studies involving relevant routes of exposure to humans should be emphasized in evaluating the potential human carcinogenicity of the various nickel species.

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

- Likely explanations for apparent discrepancies in the results of different epidemiological studies—*e.g.*, differences in the principal nickel species to which the workers were exposed, differences in levels of exposure, differences in possible confounding factors like smoking or the presence of other occupational carcinogens, etc.
- The relevance of the routes of exposure used in animal studies—with greater emphasis being placed on results from studies employing routes of administration that are of relevance to human exposure scenarios.
- The likely mechanism of action for nickel-related carcinogenesis and the implications that this may have for whether a particular nickel species is potentially a direct-acting carcinogen or, at most, an agent that may enhance an organism's response to exposure to other carcinogenic agents.