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April 9, 2003

*Received
April 11, 2003*

Associate Director for Communications
Office of the Director
National Institutes of Health
Building 1, Room 344
9000 Rockville Pike
Bethesda, MD 20892

Re: Correction of Information Request

Dear Sir/Madam:

INTRODUCTION

Pursuant to the Data Quality Act¹ and the implementing Guidelines issued by the Office of Management and Budget (“OMB Guidelines”),² the Department of Health and Human Services (“HHS Guidelines”),³ and the National Institutes of Health (“NIH Guidelines”),⁴ I am submitting this information quality request, seeking the correction of information disseminated by the National Toxicology Program (“NTP”) in the Tenth Report on Carcinogens (“10th RoC”), which was made available to the public on December 11, 2002.⁵ This request for correction of information is being submitted on behalf of the Nickel Development Institute (“NiDI”), the Nickel Producers Environmental Research Association (“NiPERA”), and Inco, United States, Inc. (“Inco”). NiDI and NiPERA are organizations of the world’s primary nickel producers.

¹ Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (P.L. 106-554).

² 67 Fed. Reg. 8452 (February 22, 2002).

³ Guidelines for Ensuring the Quality of Information Disseminated to the Public (<http://www.hhs.gov/infoquality/part1A-9-20.htm>).

⁴ Guidelines for Ensuring the Quality of Information Disseminated to the Public (<http://www.hhs.gov/infoquality/NIHinfo2.htm>).

⁵ The 10th RoC appears on the NIH website at <http://ehp.niehs.nih.gov/roc/toc10.html>.

Inco's parent company, Inco Limited, a Canadian corporation, is a member of NiDI and NiPERA.

The material proposed for correction involves the background discussion of Nickel Compounds and Metallic Nickel published in the 10th RoC, which listed Nickel Compounds as *known to be human carcinogens* and Metallic Nickel as *reasonably anticipated to be a human carcinogen*. Inco and other members of NiDI and NiPERA are affected by the dissemination of this material because the inaccurate, incomplete, and biased information will lead to unjustified regulatory burdens on nickel producers and users and will cause nickel to be viewed as a less desirable material for use in industrial and consumer applications—thereby adversely affecting the business of nickel producers and users, including NiDI and NiPERA member companies.

As discussed below, the discussion accompanying the 10th RoC listings of Nickel Compounds and Metallic Nickel does not comply with the OMB Guidelines—or with the HHS and NIH Guidelines—in the following respects:

1. It does not comply with the “objectivity” requirement of the OMB Guidelines because:
 - a. It is not “presented in an accurate, clear, complete, and unbiased manner”⁶; and
 - b. It does not present “accurate, reliable, and unbiased information.”⁷
2. Although the 10th RoC presents “influential” scientific information relating to an analysis of risks to human health allegedly posed by exposure to nickel compounds and metallic nickel,⁸ it fails to comply with the science quality

⁶ OMB Guidelines, section V.3.a., 67 Fed. Reg. at 8459.

⁷ *Id.*, section V.3.b. Because the discussion appearing in the 10th RoC has not been subjected to formal, independent, external peer review, it cannot be presumed to be of acceptable objectivity.

⁸ There is little doubt that the RoC constitutes “influential” scientific information, because it is one of NIH’s “most visible publications.” *See* NIH Guidelines, section V.2.d. Accordingly, NTP “can reasonably determine that dissemination of the information [contained in the 10th RoC] will have . . . a clear and substantial impact on important public policies or important private sector decisions.” OMB Guidelines, section V.9, 67 Fed. Reg. at 8460. For example, a substance listed in the RoC as a “known” or “reasonably anticipated” human carcinogen must be considered to be a carcinogen under the Occupational Safety and Health Administration’s Hazard Communication Standard, 29 C.F.R. § 1910.1200, Appendix A, and must be listed as known to the state to cause cancer under § 12306 of California’s “Proposition 65” regulations, 22 CCR § 12306. The discussion of carcinogenicity of nickel compounds and metallic nickel in the 10th RoC also can have a substantial impact on materials selection decisions in the private sector, on consumer product choices, and on measures taken to control nickel-related exposures in the workplace. In addition, the 10th RoC’s discussion of carcinogenicity of nickel compounds and metallic nickel can “have important consequences for specific . . . substances [*i.e.*, nickel and

principles established by Congress in the Safe Drinking Water Act Amendments of 1996, as required by the OMB Guidelines,⁹ in that:

- a. It does not use the best available peer reviewed science;
- b. It does not identify studies that fail to support the carcinogenic effect; and
- c. It is not comprehensive, informative, and understandable.¹⁰

DISCUSSION

A. The “Objectivity” Requirement

The discussion of Nickel Compounds and Metallic Nickel in the 10th RoC is not “presented in an accurate, clear, complete, and unbiased manner.”¹¹ Moreover, the information that is presented is not “accurate, reliable, and unbiased.”¹² As discussed in the Comments of NiPERA submitted to Dr. Kenneth Olden of NTP on February 21, 2003 (copy attached as Appendix A), the main problems in this regard are:

- (1) the failure to acknowledge that there is no evidence of carcinogenicity of nickel compounds by relevant routes of exposure other than inhalation;
- (2) the failure to take account of the physical form (*e.g.*, powder vs. massive solid) in evaluating the carcinogenic potential of nickel metal; and
- (3) the biased and selective presentation of the human and animal studies on which the listing for soluble nickel compounds is based.

1. The 10th RoC is unaccountably silent on the question of route of exposure. NTP identifies no animal studies by the oral or dermal routes of exposure that have resulted in cancer, and with good reason—there are none. At the same time, it neglects to mention that all the animal studies conducted thus far via the oral route have been negative. And it fails to point out that the only evidence in human studies of a consistent association between exposure to certain nickel compounds and an increased risk of cancer involves the respiratory tract. In combination,

nickel compounds], products [*i.e.*, those containing—or manufactured in a process using—nickel or nickel compounds], or firms [*i.e.*, those that produce or use nickel or nickel compounds].” NIH Guidelines, section VII.

⁹ See OMB Guidelines, section V.3.b.ii.C, 67 Fed. Reg. at 8460.

¹⁰ See 67 Fed. Reg. at 8457-58; see also NIH Guidelines, section V.2.d.

¹¹ OMB Guidelines, section V.3.a., 67 Fed. Reg. at 8459.

¹² *Id.*, section V.3.b.

these results indicate that inhalation is the only relevant route of exposure as far as any nickel-related cancer risk is concerned. Yet, the 10th RoC is completely silent on this point, thereby presenting a seriously incomplete picture of potential nickel-related carcinogenicity and misleading the public as to the nature of the potential risk. Moreover, NTP's failure to distinguish between the inhalation and oral routes of exposure in evaluating the potential carcinogenicity of nickel and nickel compounds reflects a misguided position on a major policy question that is likely to be of strong interest to U.S. EPA, which currently is revising its Integrated Risk Information System ("IRIS") file on soluble nickel compounds.¹³

2. The 10th RoC also is misleading in its failure to make clear that the "reasonably anticipated" listing of Metallic Nickel, which is based solely on certain animal studies, depends on the physical form in which the nickel metal is present. The "reasonably anticipated" listing appears to be based on animal studies in which *nickel powders* were administered via intratracheal instillation. NTP should have made clear that the listing does not apply to *massive forms of nickel* such as, for example, a nickel-plated chair leg. There is no carcinogenic risk associated with exposure to *massive solid* forms of metallic nickel, and those are the main types of nickel exposures that the general population encounters. The failure to point this out makes the discussion of metallic nickel incomplete, inaccurate, and biased.

3. By the same token, in the brief discussion of animal studies, NTP makes no reference whatsoever to the negative *inhalation* results for nickel sulfate hexahydrate obtained in its own animal bioassay (NTP 1996), or to the negative results found in other animal carcinogenicity studies of soluble nickel compounds employing a relevant route of exposure (*oral ingestion*)—*e.g.*, Schroeder *et al.* (1974) & (1964); Schroeder and Mitchener (1975); Ambrose *et al.* (1976).¹⁴ Instead, the 10th RoC highlights the kidney tumors produced by intraperitoneal injection of nickel acetate (when sodium barbital also was present) and the pituitary tumors seen only in a transplacental, intraperitoneal study at highly toxic doses. This highly skewed selection of studies—ignoring those involving relevant routes of exposure and emphasizing those whose relevance to humans is highly problematic—raises serious questions about the objectivity and scientific integrity of the document.

4. Another example of inaccuracy in the document is the statement that the Andersen *et al.* (1996) study of nickel refinery workers in Norway showed that exposures to "*soluble nickel alone*" resulted in excess cancer risks (fourth sentence in paragraph 2 of the Nickel Compounds section). In fact, workers at this Norwegian refinery always had mixed exposures to soluble and insoluble nickel compounds, as well as to cigarette smoking, arsenic, and acid mists

¹³ For this reason—and because the 10th RoC's discussion of Nickel Compounds and Metallic Nickel involves "influential" information—this Correction of Information Request should be forwarded to OMB. See Memorandum for the President's Management Council from John D. Graham, *Executive Branch Implementation of the Information Quality Law*, p. 3 (Oct. 4, 2002).

¹⁴ All references to the literature cited in this letter are identified in the 10th RoC itself or in the References section of attached Appendix A.

(all of which are respiratory carcinogens). Indeed, 98% of lung cancer cases in this cohort occurred among smokers, and none of the lung cancer cases was exposed solely to soluble nickel. The 10th RoC's statement to the contrary is simply inaccurate. At the same time, the 10th RoC fails to mention the negative, albeit smaller, study of nickel platers who were exposed almost exclusively to soluble nickel without many of the confounders found in the refinery study (Pang *et al.*, 1996). This is an example of bias—or at least, serious incompleteness—in the presentation of relevant human data.

5. Additional inaccuracies occur in the discussion of welding studies, which the 10th RoC cites as examples of occupations where exposure to nickel compounds can be viewed as causing increased cancer risks. Thus, the Report states: “Nickel exposure in mild steel workers is associated with cancer (carcinoma) of the trachea, bronchus and lung in some cases (Simonato, 1991).” This statement is incorrect on several counts. First, while *stainless steel alloys* may contain 4.5% - 35% nickel, *mild steel* is almost completely devoid of nickel, with a maximum nickel content limit of 0.2%. Therefore, mild steel welders are expected to have negligible exposures to nickel. Second, in their study of welders, Simonato *et al.* (1991) found that excess lung cancer mortality was **not** associated with duration of employment or cumulative exposure to total fume, total chromium, or nickel. This study involved one of the largest cohorts studied to date, consisting of ~11,000 welders of stainless steel, mild steel, and shipyard welders. Further analyses of this cohort (Gerin *et al.*, 1993) showed no trend for lung cancer risk for three categories of nickel exposure. Other studies of welders (Moulin *et al.*, 1993; Danielsen *et al.*, 1996; Hansen *et al.*, 1996; Moulin, 1997) likewise have failed to show an increased risk of lung cancer and/or a causal association between welding on nickel-containing alloys and cancer. Becker (1999) suggests that when increased respiratory cancer risks are seen in welders, this risk can most readily be accounted for by exposure to asbestos. Thus, the 10th RoC's discussion of welding studies that supposedly indicate a nickel-related increased cancer risk is both inaccurate and seriously incomplete.

6. The 10th RoC's characterization of the available human studies as being “*inadequate*” for evaluating the carcinogenic effects of metallic nickel in humans is grossly misleading. 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 studies. While it is true that metallic nickel exposures, on average, were low (< 0.5 mg Ni/m³, ranging up to averages of 1.5 mg Ni/m³), 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, the exposure levels and the 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 also have been negative. In a study of hydrometallurgical 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/m³ (Egedhal *et*

al., 2001). 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 $> 5 \text{ mg Ni/m}^3$.

In light of these studies—none of which showed an association between inhalation exposure to metallic nickel particles and increased risk of respiratory cancer—it is misleading (and suggestive of bias) to say that the human evidence for the carcinogenicity of nickel metal is “*inadequate*.” A more accurate statement is that occupational studies indicate that inhalation exposure to metallic nickel dust in the workplace does not create an increased risk of respiratory cancer.

7. The 10th RoC is inaccurate in its presentation of exposure information as well. Thus, it states: “The average daily oral intake of nickel was estimated at 300-600 μg (HSDB, 2001).” This is indeed what the HSDB says, but it quotes an EPA notice from 1983, 48 Fed. Reg. 45502 (Oct. 5, 1983), which itself provided no reference for this estimate. More appropriate references for oral intake would be ATSDR (1997), which places the average dietary intake of nickel at 170 $\mu\text{g/day}$, or Pennington and Jones (1988), which reports that nickel intake by sex and age groups ranges from 69-163 $\mu\text{g/day}$. These values are significantly lower than the one cited by NTP.

8. The inaccuracy, lack of clarity, and unreliability of the 10th RoC continues in the discussion of regulations applicable to metallic nickel and nickel compounds. For example, NTP states that “RCRA regulates nickel and nickel compounds as hazardous wastes.” What NTP means by this is unclear, but the statement is incorrect or, at the very least, misleading. It seems to imply that any wastes containing nickel or nickel compounds are regulated as hazardous wastes under RCRA. That is incorrect. Perhaps NTP only means to suggest that if a waste contains nickel or nickel compounds above a certain concentration in its total composition or in leachate generated from the waste using RCRA’s Toxicity Characteristic Leaching Procedure (“TCLP”), the waste is regulated as “hazardous.” But that, too, is erroneous. The RCRA regulations do not include a content-based or TCLP-based toxicity characteristic for nickel. The contrary implication in the 10th RoC is inaccurate, and the statement itself is unclear and unreliable.

9. Also inaccurate is the statement that the Superfund Amendments and Reauthorization Act (“SARA”) “establishes threshold planning quantities [for nickel and nickel compounds].” SARA does not establish a threshold planning quantity for metallic nickel, and the only nickel compound for which it establishes a threshold planning quantity is nickel carbonyl.¹⁵

10. The 10th RoC’s discussion of the regulations applicable to “Metallic Nickel” is particularly confused and unreliable. Virtually everything referred to in this section applies not to *metallic nickel*, but to one or more *nickel compounds*.

¹⁵ See 40 C.F.R. Part 355, Appendix A.

The foregoing are examples of the inaccuracy, incompleteness, unreliability, and bias that characterize both the manner in which information relating to Nickel Compounds and Metallic Nickel is presented in the 10th RoC and the substance of the information itself. Other examples are set forth in attached Appendix A. This material should be corrected as indicated above and in the attached Appendix.

B. The Safe Drinking Water Act Amendments Science Quality Requirement

The 10th RoC also fails to comply with the science quality principles established by Congress in the Safe Drinking Water Act Amendments of 1996—because it does not use the best available peer reviewed science, does not identify studies that fail to support the asserted carcinogenic effects of metallic nickel and nickel compounds, and is not comprehensive, informative, and understandable.

Several examples of these shortcomings are discussed in section A above, such as—

- the failure to mention that all the animal studies conducted thus far via the oral route have been negative;¹⁶
- the failure to note that massive solid forms of metallic nickel do not present a carcinogenic risk;¹⁷
- the failure to reference the negative results for nickel sulfate hexahydrate obtained via *inhalation* in NTP's own animal bioassay and in other animal studies of soluble nickel compounds employing a relevant route of exposure (*oral ingestion*);¹⁸
- the failure to mention the recent welding studies that found no increased risk of lung cancer and/or no causal association between increased cancer risk and welding with nickel-containing alloys;¹⁹ and
- the failure to reference the substantial number of studies in the nickel-using and nickel-producing industries in which no nickel-related excess respiratory cancer risks were found.²⁰

By contrast, the 10th RoC makes much of two animal studies that have little or no relevance to potential human cancer risk. The first is a study by Kasprzak *et al.* (1990) in which

¹⁶ See *supra* section A.1.

¹⁷ See *supra* section A.2.

¹⁸ See *supra* section A.3.

¹⁹ See *supra* section A.5.

²⁰ See *supra* section A.6.

male F 344 rats (but not female rats) exposed to *both* soluble nickel and sodium barbital developed kidney tumors, whereas *kidney tumors were not seen in male rats exposed to soluble nickel alone*. Subsequent work by some of these authors has confirmed that sodium barbital is not just a tumor promoter, but a complete kidney carcinogen (Kurata *et al.*, 1993). The 10th RoC ignores this information regarding the carcinogenicity of sodium barbital and overlooks the fact that the kidney tumors (seen only in male rats) could be related to an alpha-2 microglobulin mechanism.²¹ Male F 344 rats are susceptible to this phenomenon, but female rats and humans are not. The failure to acknowledge these points makes the 10th RoC's discussion of animal studies involving soluble nickel incomplete and uninformative.

A similar problem characterizes the 10th RoC's discussion of the second study on which NTP relies as animal evidence for the carcinogenicity of nickel compounds, an intraperitoneal transplacental study by Diwan *et al.* (1992). This is the only one out of a dozen studies (some of them by oral and inhalation routes of exposure) in which exclusive exposure to a soluble nickel compound resulted in increased tumor induction. But in the Diwan study, the observed increases in the pituitary tumors in pups of dams exposed to high levels of nickel acetate may be explained by a hormonal disruption due to the toxic effects of the Ni (II) ion (as evidenced by the 88% mortality in the pups). It has been shown that in the rat, pituitary tumors can occur as a result of hormonal disruption (Mennel, 1978). Failure to observe pituitary tumors in any other study with soluble and insoluble nickel compounds via the same or other routes of exposure (transplacental, intraperitoneal, oral, and inhalation) is consistent with this explanation. Yet the 10th RoC makes no mention of this point, greatly diminishing its informative value.

In sum, just as it fails to meet the "objectivity" requirements of the OMB Guidelines, the 10th RoC's discussion of Nickel Compounds and Metallic Nickel falls short of complying with the science quality principles established by Congress in the Safe Drinking Water Act Amendments of 1996.

CONCLUSION


The 10th RoC's discussion of Nickel Compounds and Metallic Nickel fails to comply with requirements of the Data Quality Act, as implemented in the OMB, HHS, and NIH Guidelines. NiDI, NiPERA, and Inco request that the material identified above and in attached Appendix A be corrected (as indicated herein) and that an appropriately revised discussion of Nickel Compounds and Metallic Nickel be published and disseminated as a correction to the 10th RoC.

Representatives of NiDI, NiPERA, and Inco would be pleased to meet with NTP officials to discuss any of the points made in this Correction of Information Request.

²¹ Work by Kurata *et al.* (1994) determined that sodium barbital increased the incidence of kidney tumors in male rats through an alpha-2 microglobulin mediated pathway.

Sincerely,

/s/


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