

WILMER, CUTLER & PICKERING

2445 M STREET, N.W.
WASHINGTON, DC 20037-1420

TELEPHONE +1 (202) 663 6000
FACSIMILE +1 (202) 663 6363
WWW.WILMER.COM

WASHINGTON
NEW YORK
BALTIMORE
NORTHERN VIRGINIA
LONDON
BRUSSELS
BERLIN

NEIL J. KING
(202) 663-6061
NEIL.KING@WILMER.COM

November 17, 2003

Associate Director for Communications
Office of the Director
National Institutes of Health
Building 1, Room 344
1 Center Drive
Bethesda, MD 20892

Re: Information Quality Appeal

Dear Sir/Madam:

On April 9, 2003—on behalf of the Nickel Development Institute (“NiDI”), the Nickel Producers Environmental Research Association (“NiPERA”), and Inco, United States, Inc. (“Inco”)—I submitted an information quality request, seeking the correction of certain information disseminated by the National Toxicology Program (“NTP”) as part of its discussion of “Nickel Compounds and Metallic Nickel” in the Tenth Report on Carcinogens (“10th RoC”). A copy of that information correction request is attached hereto as Attachment 1. It was submitted pursuant to the Data Quality Act^{1/} 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/} After a series of delays, Dr. Christopher J. Portier, Associate Director of NTP, responded to my request for correction of information by letter dated October 24, 2003 and received on October 27, 2003. A copy of Dr. Portier’s letter is attached hereto as Attachment 2.

^{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>).

With the limited exception of certain statements regarding the daily oral intake and regulatory treatment of nickel—which Dr. Portier indicated might be corrected in the next edition of the RoC, whose publication presumably is 18 months away—the response asserts that the discussion of “Nickel Compounds and Metallic Nickel” in the 10th RoC complies fully with the applicable Guidelines. Accordingly, my request for correction of information was denied, and I was advised of my right to appeal the agency’s decision within 30 days of receiving the response.

This letter constitutes an appeal of that decision. I am taking the appeal because I feel that NTP’s response was defensive, evasive, hyper-technical, and mistaken on a number of critical points.^{5/} In my view, it violates both the letter and the spirit of the Data Quality Act and the OMB Guidelines. If left to stand, it would turn the information correction request process into a charade.

Background

Before addressing some of the specific points on which I believe Dr. Portier’s response is mistaken or inadequate, I want to respond to his preliminary remarks regarding the nature of the RoC listing process and his feeling that “many of the concerns mentioned in [my] request for correction are addressed in the background documents” for Nickel Compounds and Metallic Nickel that were prepared as part of that process.^{6/} According to Dr. Portier, NTP considers the background documents to be supporting documentation for the information contained in the RoC. And, as he points out, an opportunity to comment on the background documents was provided during the periods in which the potential RoC listings of Metallic Nickel and Nickel Compounds were being considered. NiPERA, NiDI, and Inco took advantage of that opportunity to file comments. This, however, does not mean that “many of the concerns mentioned in [my] request for correction are addressed in the background documents”; nor does it excuse the failure of the RoC itself to comply with the Information Quality Guidelines. In this regard, two points should be emphasized.

First, although NiPERA, NiDI, and Inco commented on the draft background documents, those comments were never incorporated into revised or updated versions of the documents; nor were they addressed in any other way. The “Draft Background Document for Metallic Nickel and Certain Nickel Alloys” dated December 2000 has never been revised; the version currently posted on the NTP website is the same exact December 2000 “Draft” on which NiPERA, NiDI, and Inco commented at the time. The same is true of the earlier “Draft Background Document for Nickel Compounds,” which was prepared in October 1998 and never revised thereafter.

^{5/} The defensive and evasive character of the response is evident even with respect to the oral intake value and the regulatory points that Dr. Portier indicated might be corrected in the next edition of the RoC. Rather than acknowledging that NTP was in error, he identified the source for the oral intake value without responding to my observation that it was way out of date, and he laid the blame for any inaccuracy as to the regulatory points on other agencies (like EPA), without saying whether or not the points I had made were correct. See Portier letter at 6.

^{6/} See *id.* at 2-3.

Thus, the concerns NiPERA, NiDI, and Inco expressed have not been addressed in the Background Documents, because the Background Documents have not been changed since the time those concerns were first expressed in 1998 and 2000.

Second, even if the Background Documents had been revised to address our concerns, that would not excuse the failure of the 10th RoC to comply with the Information Quality Guidelines. The Background Documents are separate from the RoC itself, and they were released years before the 10th RoC was disseminated—almost three years in the case of Metallic Nickel and almost five years in the case of Nickel Compounds. Moreover, the Background Documents and the RoC are intended for different audiences. The Background Documents serve as the informational basis for the recommendations of the RoC review committees,^{7/} while the RoC itself is prepared for distribution to Congress and to interested members of the public and the broader scientific and regulatory communities. Thus, both temporally and in terms of the intended audiences, dissemination of the RoC is very different from dissemination of the Background Documents. NTP cannot defend the 10th RoC's failure to meet the "objectivity" requirement of OMB's Guidelines in 2003 by asserting that information *contained in two entirely separate documents that were disseminated to a different audience three to five years earlier* would have satisfied the Guidelines if they had been in effect at the time. The 10th RoC must stand on its own in this regard. The fact that NTP considers the background documents to be "supporting documentation for the information [presented] in the . . . RoC"^{8/} does not excuse a failure of the RoC itself to meet the "objectivity" standard of OMB's Guidelines.^{9/}

With the foregoing observations as background, I will now explain why I find NTP's response to specific points raised in my information quality request to be inadequate.

Discussion

1. The first point noted in my April 9 letter was that, in combination, the results of the human and animal studies 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.

In response, Dr. Portier states that NTP's "listing criteria do not require demonstration of carcinogenicity by multiple routes of exposure to experimental animals or humans."^{10/} That may

^{7/} See *id.* at 1.

^{8/} See *id.* at 2.

^{9/} Nor can the 10th RoC's failure to comply with the OMB Guidelines be excused by noting that background documents are "intended to be concise, comprehensive and unbiased." See *id.* at 1. Is this meant to imply that the RoC, by contrast, is intended to be "wordy" and "biased"?

^{10/} *Id.* at 3.

be so, but it does not justify the failure to mention that no evidence of increased cancer risk has been found via the oral or dermal routes of exposure. I did not ask that the listing decision for nickel be reversed. What I asked is that the 10th RoC avoid presenting a one-sided and misleading picture of the potential cancer hazard. This is important, because the RoC is supposed to present information on the nature of exposure to the listed substances,^{11/} and for nickel, it says that “[e]nvironmental exposure . . . occurs through inhalation, ingestion, and dermal contact.”^{12/} By failing to note that only the inhalation route has shown evidence of an increased cancer risk, the 10th RoC misleads the public as to the nature of the potential exposure-related hazard—leaving the impression, for example, that dermal contact with a nickel plated object presents a cancer hazard.^{13/}

2. My second point was that the 10th RoC is misleading in its failure to make clear that the “reasonably anticipated” listing of Metallic Nickel depends on the physical form in which the nickel metal is present. This listing appears to be based on animal studies in which *nickel powders* of inhalable size 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, that cannot possibly be inhaled. This is important because exposures to *massive solid* forms of metallic nickel are the main types of metallic nickel exposures that the general population encounters. Failing to point this out makes the discussion of metallic nickel in the 10th RoC incomplete, inaccurate, and biased.

In response, Dr. Portier quotes the Introduction to the 10th RoC, which states that “cancers resulting from exposures to the listed substances may require exposures for prolonged periods of time” and that “the carcinogenic hazard . . . to any one person depends on many factors . . . [including] the amount and duration of exposure to the substance, an individual’s susceptibility to the carcinogenic action of the substance, and the intrinsic carcinogenicity of the substance.”^{14/} None of these factors addresses the point I made regarding the absence of a qualitative cancer hazard associated with exposure to *non-inhalable massive* forms of metallic nickel, precisely the forms to which the general public is most likely to be exposed. Nor is this a question of identifying an acceptable level of risk, which, as Dr. Portier correctly notes, “is the

^{11/} See 10th RoC at I-1.

^{12/} *Id.* at III-164.

^{13/} Dr. Portier notes that the Background Documents contain a discussion of the positive and negative studies by the various routes of administration. Portier letter at 3. That may be so. As noted above, however, the fact that such information can be found in *other documents* is irrelevant. The 10th RoC was disseminated to a different audience and at a different time. If the information *it* presents is not accurate, complete, and unbiased (which, on the route of exposure issue, it is not), the inclusion of more accurate, complete, and unbiased information in other publications (such as the Background Documents) does not save the RoC from violating the “objectivity” requirement of OMB’s Guidelines.

^{14/} Portier letter at 3.

purview of regulatory agencies.”^{15/} The point is that non-inhalable massive forms of metallic nickel *do not present a cancer hazard*, but a reader of the 10th RoC would come away with the opposite impression, because the information presented is seriously incomplete on this critical point.

3. My third point was that in its discussion of animal studies, the 10th RoC makes no reference whatsoever to the negative *inhalation* results for nickel sulfate hexahydrate obtained in NTP’s 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*).^{16/} 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. I observed that 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.

In response, Dr. Portier notes that the RoC “contains a brief description of the data supporting the listing, not a complete presentation of all of the evidence” (an understatement, if ever there was one), and he goes on to describe various alleged observations and conclusions of the RoC review committees relating to the toxicity and carcinogenicity of soluble nickel compounds.^{17/} No citations to these alleged observations and conclusions of the review committees are provided, so there is no way for me to determine whether what Dr. Portier says in that regard is accurate. In any event, it is irrelevant—because I did not ask that the listing decision be reversed, only that the information presented in the 10th RoC be “objective.” Dr. Portier’s statements as to what the review committees may have thought when they considered the entire body of evidence does not justify the highly skewed selection of studies that NTP has presented in the 10th RoC.

Nor is it justified by NTP’s desire to include in the RoC only “a brief description of the data supporting the listing.” If that is all NTP intends to do, why bother discussing the human and animal studies at all? If highly significant studies by the most relevant routes of exposure are to be excluded from the discussion because the results were not positive, what value do the summary profiles have? Why not simply publish the listing decisions and leave it at that? Including a completely one-sided and biased discussion of underlying studies does not provide useful or objective information to the reader. Instead, it leaves a misleading impression that *all* the evidence supports the view that the listed substance is carcinogenic by all routes of exposure

^{15/} *Id.*

^{16/} Unless specifically set forth herein, all references to the literature cited in this appeal letter are identified in the 10th RoC itself or in the References section of Appendix A attached to my letter of April 9, 2003.

^{17/} Portier letter at 3-4.

that might be relevant for humans. That certainly is not the case for metallic nickel and soluble nickel compounds, but the reader of the 10th RoC would never know it.

4. My fourth point was that the 10th RoC incorrectly states 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—when, in fact, workers at that refinery always had mixed exposures to soluble and insoluble nickel compounds, as well as to cigarette smoking, arsenic, and acid mists (all of which are respiratory carcinogens).

In response, Dr. Portier quotes the full statement in the 10th RoC, which reads as follows: “An additional study has shown that exposure of nickel refinery workers to soluble nickel compounds alone or in combination with other forms of nickel results in significant excess risks for lung and nasal cancer and that smoking and nickel exposure have a multiplicative effect.”^{18/} This statement, he asserts, “is accurate,” but he never explains why. While the authors of the Andersen *et al.* paper did state that was the case, the paper itself and a more recent paper by Grimsrud *et al.*, (2000)^{19/} show that the Norwegian refinery workers were not exposed to soluble nickel in the absence of concurrent exposure to other forms of nickel. As Andersen and coworkers acknowledge, “workers [in nickel refineries] are not exposed exclusively to either soluble or insoluble forms [of nickel].”^{20/} And the exposures of this cohort, as reported in Grimsrud *et al.* (2000), were always mixed. Thus, Dr. Portier’s unexplained claim of accuracy for the 10th RoC’s statement that excess risks of lung and nasal cancer were found among refinery workers exposed to soluble nickel alone does not constitute an adequate response to the point I raised.

5. My fifth point was that the 10th RoC unjustifiably indicates that nickel exposures have been shown to cause increased cancer risks among welders. In particular, the Report states: “Nickel exposure in mild steel welders is associated with cancer (carcinoma) of the trachea, bronchus and lung in some cases (Simonato, 1991), although subjects in these studies also were exposed to the known carcinogen chromium, which complicates the results.” I noted that *mild steel* is almost completely devoid of nickel (with a maximum nickel content limit of 0.2 percent), so that nickel exposures of mild steel welders would likely be negligible. And I pointed out that Simonato *et al.* (1991) found that excess lung cancer mortality was *not* associated with cumulative exposure to nickel. Accordingly, the 10th RoC’s suggestion that the study of mild steel welders by Simonato (1991) indicates a nickel-related increased cancer risk is inaccurate.

In response, Dr. Portier quotes a statement in the Background Document for Nickel Compounds—which, as noted earlier, does not excuse a lack of objectivity in the 10th RoC

^{18/} *Id.* at 4.

^{19/} Grimsrud, T.K., Berge, S.R., Resmann, F., Norseth, T., Andersen, A. (2000). Assessment of historical exposures in a nickel refinery in Norway. *Scand J Work Environ Health* **26(4)**, 338-345.

^{20/} Andersen *et al.* (1996) at 708.

itself—and simply asserts that the statement in the 10th RoC quoted above “is accurate and reflects what has been reported in the literature.”^{21/} But, as pointed out in my April 9 letter, the implication in the 10th RoC that nickel exposure caused increased cancer risks in the mild steel welders studied by Simonato is *not* accurate and does not reflect what has been reported in the literature. While I do not quarrel with Dr. Portier’s suggestion that it may be appropriate for NTP to consider listing occupational exposure to welding fumes in the RoC,^{22/} I do take exception to NPT’s use of this welder study as evidence for the carcinogenicity of nickel.

6. My sixth point was that the 10th RoC is misleading when it states: “The available studies of the carcinogenicity of metallic nickel in humans are inadequate for an evaluation.” I noted that more than 40,000 workers from various nickel-using industry sectors have been examined for evidence of carcinogenic risk due to exposure to metallic nickel (and, in some instances, accompanying oxidic nickel compounds),^{23/} yet, no nickel-related excess respiratory cancer risks were found in any of these studies. I acknowledged that, on average, metallic nickel exposures in these studies were relatively low (<0.5 mg Ni/m³, though ranging up to averages of 1.5 mg Ni/m³). As I pointed out, however, these exposures are far higher than those found in the ambient air (an average of 2.2 *nanograms*/m³)^{24/} and are at least as high or higher than metallic nickel exposures found in occupational settings today. I went on to observe that studies of nickel-producing workers also have been negative—citing Egedhal *et al.*, 2001 (hydrometallurgical refining workers exposed to metallic nickel concentrations ranging from 0.2 to 49 mg Ni/m³), and ICNCM, 1990^{25/} (two refinery cohorts totaling ~ 6,000 workers showed no evidence of increased lung or nasal cancer risks associated with metallic nickel even though exposures to metallic nickel in some departments within these refineries were >5 mg Ni/m³). In light of these studies, I said it was misleading (and suggestive of bias) to describe the human studies as being “inadequate for an evaluation.”

In response, Dr. Portier makes two points: (1) These studies have low power for detecting a direct effect of metallic nickel—either because of low metallic nickel exposures or

^{21/} Portier letter at 4.

^{22/} *Id.* at 5.

^{23/} Enterline and Marsh, 1982; Cox *et al.*, 1981; Cragle *et al.*, 1984; Arena *et al.*, 1998; Moulin *et al.*, 2000.

^{24/} See U.S. EPA, Final National-Scale Air Toxics Assessment for 1996, at <http://www.epa.gov/ttn/atw/nata/index.html>.

^{25/} ICNCM (International Committee on Nickel Carcinogenesis in Man), 1990. Report of the International Committee on Nickel Carcinogenesis in Man. *Scand. J Work Environ Health* **16**, 1-84.

small numbers of exposed workers; and (2) The worker populations also were exposed to other carcinogens or to nickel compounds that are believed to be carcinogenic.^{26/}

As to his first point, while the power of most of these studies to demonstrate individually a direct carcinogenic effect of metallic nickel may be low due to small cohort sizes, the studies are numerous, were conducted in a wide variety of nickel producing and using industries, and are remarkably consistent in failing to detect an association between metallic nickel exposure and an increased risk of lung or nasal cancer. Moreover, one of these studies is quite large, with more than 31,000 workers in the cohort (Arena *et al.*, 2001). Dr. Portier claims the power of this study to detect an effect is limited because “exposures [sic] levels were low.”^{27/} However, because of the large size of the cohort and the large number of person-years at risk, the statistical power of the study to detect a small increased relative risk of 1.1 is more than 90 percent. Thus, the exposure levels in the Arena, *et al.* study do not significantly limit its power to detect an effect. Moreover, the exposures in this study are 5-6 orders of magnitude higher than those in the ambient air and are almost certainly as high or higher than those found in current workplaces. In addition, while relative risks in this study were higher when based on comparisons to the U.S. population than when local populations were used for comparison, Arena *et al.* point out the advantage of using local populations in this particular study as a means of controlling for risk factors that may be related to geographic variability rather than occupational exposure. Furthermore, they note that the slightly elevated risks of lung cancer found in the comparison to the U.S. population were not associated with duration of employment or length of time since first exposure—suggesting that even these small excess risks were not occupationally related.

As to Dr. Portier’s second point, the fact that workers in these cohorts also were exposed to other carcinogens or to various nickel compounds does not detract from the fact that no nickel-related excess respiratory cancer risks were found in the studies. Surely, the other agents to which the workers were exposed were not antagonistic to (or protective against) a potential carcinogenic effect of metallic nickel.

In sum, while the available studies of workers exposed to metallic nickel are not definitive, it is misleading to say they are “inadequate for an evaluation.” They can be evaluated—at least to the extent of saying they do not indicate that inhalation exposure to metallic nickel in the workplace creates an increased risk of respiratory cancer. Other scientific bodies have reached that judgment. For example, the American Conference of Governmental Industrial Hygienists (“ACGIH”) has classified metallic nickel in category A5, indicating that it is “Not Suspected as a Human Carcinogen.”^{28/} NTP’s dismissive characterization of the human

^{26/} Portier letter at 5.

^{27/} *Id.*

^{28/} See ACGIH, Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices, 2003, pp. 43, 70. This determination was made “on the basis of properly conducted epidemiologic studies in humans,” which ACGIH describes as “studies [that] have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of

studies as “inadequate” omits highly relevant information necessary to provide important context to its listing of metallic nickel as “reasonably anticipated to be a human carcinogen,” a listing that was made on the basis of animal studies involving routes of exposure that have no direct relevance for humans.

7. Finally, my April 9, 2003 letter noted that the 10th RoC 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. Examples of all these points were presented in my letter.

In response, Dr. Portier states that under the OMB Guidelines, the Safe Drinking Water Act (“SDWA”) science quality principles apply only to *quantitative risk assessment* documents, not to a document like the RoC that presents the results of scientific evaluations regarding the carcinogenic hazard of the listed substances.^{29/} His position on this point reflects an extremely narrow and restrictive reading of section V.3.b.ii.C of the OMB Guidelines, which directs agencies to adopt or adapt the SDWA science quality principles for information regarding the “analysis of risks to human health, safety and the environment.”^{30/} I do not believe that, by using this phrase, OMB intended to limit application of the SDWA science quality principles to quantitative risk assessments, leaving agencies free to ignore these principles when they make all other science-based determinations—including determinations, like the identification of a chemical as a human carcinogen, that will have enormous regulatory, public health, and market consequences.

The carcinogenic hazard evaluation that NTP performs when it prepares the RoC is an element of “the analysis of risks to human health” to which the OMB Guidelines refer. Hazard identification is the first step of a risk assessment.^{31/} NTP’s determinations regarding carcinogenicity thus become part-and-parcel of the quantitative risk assessments that other agencies may conduct when they carry out their own regulatory functions. NTP should not be allowed to escape application of the SDWA science quality principles when it performs the

cancer to humans.” *Id.* at 70. *See also* ICNCM, 1990 (“There was no evidence [in the epidemiologic studies] that metallic nickel was associated with increased lung and nasal cancer risks. . . .”); IARC, 1990 at 410 (“There is *inadequate evidence* in humans for the carcinogenicity of metallic nickel and nickel alloys.”); ATSDR, 1997 at 54 (adopting the ICNCM conclusion that, in the human studies, “[n]o evidence was found that metallic nickel causes respiratory cancer.”).

^{29/} *See* Portier letter at 6-7.

^{30/} 67 Fed. Reg. 8452, 8460 (Feb. 22, 2002).

^{31/} *See* National Academy of Sciences/National Research Council, *Risk Assessment in the Federal Government: Managing the Process*, National Academy Press, 1983, p. 3.

first—and most critical—step of the quantitative risk assessment process, and I do not believe OMB intended such a result.

Is it really plausible that OMB meant to allow agencies to make science-based determinations of enormous consequence without using “the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices”—as the SDWA science quality principles require?^{32/} I think not. Congress, after all, did not limit application of the SDWA science quality principles to quantitative risk assessments. Instead, the EPA Administrator was directed to apply these principles “to the degree that an Agency action is based on science.”^{33/} By the same token, in making determinations regarding drinking water standards, the Administrator was mandated to “ensure that the presentation of information on public health effects is comprehensive, informative, and understandable.”^{34/} I believe OMB intended to apply those same requirements to agency-disseminated information that reflects highly significant science-based determinations, even if those determinations do not take the form of a quantitative risk assessment. NTP’s crabbed and hyper-technical reading of section V.3.b.ii.C of the OMB Guidelines must be rejected.

Conclusion

For the reasons stated above, I respectfully request that this appeal of NTP’s denial of my April 9, 2003 request for correction of information be granted; that the material identified in my April 9 letter (and in Appendix A attached to that letter) be corrected as indicated therein; and that an appropriately revised discussion of Nickel Compounds and Metallic Nickel be published and disseminated as a correction to the 10th RoC.

Sincerely,



Neil J. King
 Wilmer, Cutler & Pickering
 2445 M Street, NW
 Washington, DC 20037-1420
 Tel: (202) 663-6061
 Fax: (202) 772-6061
 E-mail: Neil.King@Wilmer.com

^{32/} 42 U.S.C. § 300g-1(b)(3)(A); *see* 67 Fed. Reg. 8457.

^{33/} 42 U.S.C. § 300g-1(b)(3)(A).

^{34/} *Id.* § 300g-1(b)(3)(B).