DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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October 27, 2004

Mr. Neil J. King
Wilmer, Cutler & Pickering
2445 M Street, N.W.
Washington, D.C. 20037-1420

Re: Information Quality Appeal submitted November 17, 2003, for Nickel in the NTP's Tenth Report on Carcinogens

Dear Mr. King:

I am responding on behalf of the National Institute of Environmental Health Sciences to your November 17, 2003, Request for Reconsideration submitted for the Nickel Development Institute, the Nickel Producers Environmental Research Association, and Inco, United States, Inc. under the NIH's "Guidelines for Ensuring the Quality of Information Disseminated to the Public" (NIH Guidelines). Your Request appealed the National Toxicology Program's (NTP) decision of October 24, 2003, on information included in its Tenth Report on Carcinogens (10th RoC) profile for the listing of Nickel Compounds and Metallic Nickel.

In considering your request, we reviewed the NIH and HHS Guidelines and the listing criteria for the RoC, as well as the scope of work for this document, as outlined in the Introduction to the 10th RoC. In addition, we reviewed the relevant scientific literature, including that information referenced in your letter and the NTP records on this particular listing. The information that was examined was used in the determination of the merits of your appeal.

We concluded that the Nickel Compounds and Metallic Nickel section of the 10th RoC complies with requirements under the NIH and HHS Guidelines. This finding is based on the following: (1) the NTP presented the scientific information on Nickel Compounds and Metallic Nickel in a manner consistent with the recommendations made by all review groups, (2) the information in the profile follows the format and protocol used in developing the RoC, (3) the listing complies with the "objectivity" requirement of the NIH guidelines, and (4) the review of Nickel Compounds and Metallic Nickel was rigorous and used the available, credible science. Further, both animal and epidemiological studies support the interpretations made in the nickel listing of the 10th RoC. However, the following clarifications will be made in the next edition of the RoC, which is expected to be released shortly: the reference to mild steel welders will be deleted; the word "alone" ['soluble nickel *alone*'] in the description of the Andersen et al. (1996) study will be deleted; the phrase "inadequate for evaluation" in the last sentence

of the section, *Metallic Nickel* will be clarified; and more specific wording will be developed about the lack of nickel studies done in animals via oral or dermal exposure routes.

Thank you for your comments regarding communication of the RoC's listing. You suggest that the RoC is misleading and does not present information as clearly and as evenly as it could. You also raise concerns about the handling of public comments received on the Background Documents. The NTP held a public meeting on January 27, 2004, at the Lister Hill Center Auditorium, National Library of Medicine, National Institutes of Health to receive public comment on the review process and the criteria used for the RoC. The NTP staff will consider your concerns together with other public comments that they received.

The rest of this letter provides (1) some background information on the RoC, (2) a point-by-point discussion of each of the seven issues raised in your letter of November 17, 2003, and (3) a reiteration of our conclusions.

*Background - RoC:* The National Toxicology Program (NTP) is charged with producing a document listing all compounds known or reasonably anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed (PHS Act, 301(b)(4) 42 U.S.C. 241 (b)(4). The current criteria for listing substances in the RoC was adopted in 1997 by the Secretary of the Department of Health and Human Services following a two-year process involving multiple review groups comprised of scientists inside and outside government.

The review of substances nominated for possible listing in (or delisting from) the RoC is conducted in an open manner with multiple opportunities for public comment from interested stakeholder groups and citizens. Although the formal process is outlined in the Introduction to the RoC, this letter highlights a few elements of the scientific review process. The NTP receives nominations for consideration for possible listing and publishes a Federal Register notice requesting public comment on them and the submission of relevant scientific information. The review of a substance for possible listing in the RoC includes evaluation by two Federal scientific panels and one non-governmental scientific panel. The NTP prepares a background document on each nomination that summarizes the available scientific information on carcinogenicity and related toxicological evidence. This background document is available to each review group and the public along with any public comment received up to that point in the review process. The review by the non-governmental panel is held in a public forum and provides an opportunity for presentation of oral and written public comment. The review groups meet sequentially and independently, evaluate the relevant scientific data and exposure to U.S. citizens on each nomination, and make a recommendation for listing in the RoC to the Director of the NTP. Upon completion of the scientific review of the nominations by the three groups, the NTP publishes their recommendations in the

Federal Register and solicits public comment. The recommendations of the three review groups and all public comments are presented to the NTP Executive Committee for review and comment. This committee provides the NTP Director its recommendation on the listing of each nomination in the RoC. The NTP Director receives the independent recommendations and all public comments, evaluates this input and any other relevant information, and develops a recommendation on each nomination. Based on the NTP Director's recommendations, NTP staff prepares the final draft of the RoC for submission to the Secretary of the Department of Health and Human Services. The NTP prepares a profile for each listing based on the information in the background document, the public comment, and the deliberations from the review panels. Each profile contains a brief description of the substance with a summary of evidence for its carcinogenicity. The RoC is issued by the Secretary of the Department of Health and Human Services.

**Item 1**:
You maintain that "the results of 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." You further state that the RoC fails "to mention that no evidence of increased cancer risk has been found via the oral or dermal routes of exposure."

Response: As a hazard identification document, the RoC focuses on relevant studies in humans, animals, and cell systems that provide evidence of carcinogenic potential. It does not assign risk to specific exposure situations, such as inhalation. Inhalation exposure is indeed a route by which nickel can be carcinogenic in humans and animals. However, there is evidence that nickel by injection can be carcinogenic in animals by routes other than inhalation. These injection routes are widely used in experimental modeling of carcinogenic response, where nickel produces local malignancies after injection. Additionally, injected nickel can have systemic carcinogenic effects. Nickel injected into pregnant rats causes malignant tumors in the offspring, thus providing evidence that *in utero* nickel exposure, originating from the maternal system, is carcinogenic in animals (Diwan et al., 1992). Further, injected nickel can cause tumors distant from the site of injection in adult animals, as evidenced by the formation of lung tumors after intraperitoneal injection in mice (Stoner et al., Poirier et al., 1994). Thus, nickel given by injection has the potential to cause cancers. The RoC correctly makes no statement that inhalation is the relevant route as far as cancer hazard is concerned. There is no evidence to indicate that all other routes are not relevant and safe based on available studies.

Our search of the literature revealed no animal studies testing nickel exposure via either oral or dermal routes. There was one study (Sunderman et al., 1977) testing the carcinogenic potential of multiple local applications of nickel subsulfide in the hamster

cheek pouch in which no tumors of the cheek pouch, oral cavity, or gastrointestinal tract were found. However, although some oral ingestion of nickel would have occurred in this study, the work was not designed to test oral exposure and would be inadequate for such an evaluation. As part of preparing the 11th RoC, NTP shall include more specific language concerning the lack of evidence regarding oral or dermal exposure routes.

**Item 2**:
Your Appeal states 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" and that "non-inhalable massive forms of metallic nickel *do not present a cancer hazard.*"

Response: The RoC listing is based in part on the fact that metallic nickel causes cancer in experimental animals. The rodent data indicate that when metallic nickel is in prolonged contact with a variety of tissues it induces cancer. Any assignment of risk based on the particular form of metallic nickel would be the purview of regulatory agencies who address the form and level of exposure. Further, the RoC indicates in the summary or listing profile, the routes of exposure used in the animal studies that led to the conclusion that it causes cancer in animals. Those routes include intratracheal, subcutaneous, intramuscular, or intraperitoneal. Therefore, the NTP has accurately summarized the exposure circumstances on which the listing is based. It must be emphasized that as a hazard identification document, the RoC does not assign risk to specific exposure situations, such as exposure to "non-inhalable massive forms of metallic nickel."

**Item 3**:
Your third point is 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*). 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." You maintain that the NTP made a "highly skewed selection of studies -- ignoring those involving relevant routes of exposure and emphasizing those whose relevance to humans is highly problematic."

Response: It is the responsibility of the RoC to serve as a hazard identification document, identifying compounds with the potential to cause human carcinogenicity. This necessary first step in the risk assessment process is not restricted to only those routes that are relevant to human exposure. Determining the actual risk levels for real-world exposures in humans occurs later in the risk assessment process, which is outside the scope of the RoC.

The mandate of the RoC is found in section 301 (b)(4) of the Public Service Act (PHS Act), as amended. It includes the following directive: "The Secretary shall publish a biennial report which contains (A) a list of all substances (i) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed; (B) information concerning the nature of such exposure and the estimated number of persons exposed to each ...." 42 U.S.C.241(b)(4). In accord with this mandate and as stated in the Introduction to the 10th RoC, ASection III, Carcinogens Profile, contains a brief description of each substance with a summary of evidence for its carcinogenicity."

A listing profile is not intended to, nor required to [based on my reading of Section 301 (b)(4)], provide a summary of all available information. The listing profile for Nickel Compounds and Metallic Nickel meets the requirements outlined in its legislative mandate under the PHS Act and the standards in the Information Quality Act and the applicable information quality guidelines.

In reviewing the study that you reference (Diwan et al., 1992), we do not think that the phrase "highly toxic doses" is a fair characterization of the research. The nickel-treated animals that developed pituitary tumors did not show evidence of overt toxicity and did not show mortality soon after birth, as one would expect from exposure to highly toxic doses. Indeed, one dosage group of pups from mothers repeatedly exposed to nickel did show evidence of overt toxicity and significant mortality after birth; this group was dropped from further consideration because of this overt toxicity. Tumors were assessed only in rats from mothers that had been given much less nickel (50% less) and that did not show early post-natal mortality.

In this study timed-pregnant F344 rats received i.p. injections of nickel acetate according to the following injection protocol:

Group 1: a single i.p. injection of 90 μmol nickel acetate/kg maternal body weight on gestation day 17 observation period: 85 weeks

Group 2: two i.p. injections of 45 μmol nickel acetate/kg maternal body weight one each on gestation day 16 and 18 observation period: 85 weeks

Group 3: four i.p. injections of 45 μmol nickel acetate/kg maternal body weight one each on days 12, 14, 16 and 18 observation period: < 1 week; not used for tumor evaluation

Group 4: control (injected i.p. with sodium acetate) Observation period: 85 weeks

Subgroups of offspring at each dose of maternal nickel acetate were given sodium barbital (subgroup B), a renal tumor promoter, to promote any renal tumors initiated by

*in utero* exposure to nickel, and compared to rats exposed *in utero* to nickel alone (subgroup A). Quoting from the Diwan et al. (1992) work: "NiAcet [nickel acetate] administered in four doses (group 3) was clearly toxic since all offspring died within 72 h [hours] after birth, and this group was deleted from the study." Tumor development was assessed only in the remaining groups of rats exposed to soluble nickel *in utero* (groups 1 and 2) and in the control rats. In the rats exposed to soluble nickel *in utero* (groups 1 and 2), the body weights were not different from control animals until very late in the study (75 weeks), when nickel-induced tumors were developing. Body weights are a well-accepted measure of generalized toxicity. Thus, the absence of suppressed body weight indicates that the doses of soluble nickel used for *in utero* exposure in the groups assessed for tumor incidence (groups 1 and 2) were well-tolerated and not "highly toxic," as stated in your letter. The animals assessed for tumor development that had been exposed to soluble nickel *in utero* (groups 1 and 2) did show reduced long-term survival; however, this was due to nickel-induced malignant pituitary and renal tumors and not generalized nickel toxicity. For these reasons, we do not agree that this study was done at "highly toxic doses." Indeed, it appears to have followed standard procedures for toxicological characterization of carcinogens.

As for the assertion that the profile contained a "highly skewed selection of studies" represented by inclusion of the Diwan et al. (1992) paper, we disagree and find it is appropriate that the 10$^{th}$ RoC mentions this work because it illustrates two important facts: (1) nickel can act as a transplacental carcinogen and (2) nickel can initiate events that respond to subsequent exposure to tumor promoters. Transplacental exposure to soluble nickel was a clear tumor initiator in the rat kidney because renal epithelial tumors occurred in rats exposed to soluble nickel *in utero* and then orally exposed after weaning to sodium barbital, a renal tumor promoter, that did not occur in control groups or groups given nickel acetate alone (Diwan et al., 1992). This finding is consistent with work also cited in the 10$^{th}$ RoC showing that nickel acetate acts as an effective renal tumor initiator in adult rats, where a single i.p. injection of nickel acetate at 90 μmol/kg followed by barbital in the drinking water produced renal cortical tumors in 67% of the rats tested, compared to 0% in controls and 4% in rats treated with nickel alone (Kasprzak et al., 1990).

Finally, it is important to emphasize transplacental exposure to environmental hazards is a common, clearly relevant, route of exposure for humans. The animals that developed tumors in the Diwan et al. (1992) study were exposed transplacentally to water-soluble nickel acetate. Although the pregnant rats were originally exposed by i.p. injection, the resulting offspring were exposed transplacentally to nickel.

**Item 4**:
Your next point is that "the 10$^{th}$ 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)."

Response: Papers by Andersen et al. (1996) and Grimsrud et al. (2000) show that some workers in the study cohort had primary exposure to soluble nickel. For example, workers in departments including copper hydrolysis, electrolyte plating, and nickel electrolysis (Grimsrud et al., 2000, p 343) had exposure to soluble nickel. Regarding other carcinogens, the most important of these, cigarette smoking, was accounted for in the Andersen paper: smoking increased lung cancer risk by 2.9-fold while smoking and nickel exposure together increased risk by 5.1-fold, compared to never smokers (Andersen et al., 1996, p 711).

Grimsrud et al. (2000) was an exposure assessment study and was meant to support and extend the etiologic analysis in Andersen et al. (1996). Aside from other nickel exposures, cigarette smoking is a major potential confounder that should be considered in studies of lung cancer (acid mists exposure is associated primarily with laryngeal cancer). Andersen et al. (1996) showed that workers exposed to soluble nickel were at increased risk of lung cancer, after accounting for exposure to nickel oxide or cigarette smoking. The dose-response for soluble nickel seen in Andersen et al. (1996) makes it unlikely that increased risk is due to confounding by other exposures (e.g., arsenic). The Grimsrud paper documented the extent of soluble nickel exposure in the same workers and showed that soluble nickel was the primary exposure for many of them. The two papers should be read and interpreted together; by doing this, major confounders are accounted for, and risk is shown to be associated with exposure to soluble nickel.

Both the International Agency for Research on Cancer (IARC) and the International Committee on Nickel Carcinogenesis, as well as NTP, concluded that exposure to soluble nickel is associated with increased risk of lung and nasal cancers. Andersen et al. (1996) showed that risk of lung cancer is related to cumulative exposure to soluble nickel even after accounting for exposure to nickel oxides (p. 710). The presence of a dose-response is strong evidence that the increased risk is causally related to exposure to soluble nickel and not due to confounding by exposure to other forms of nickel or other carcinogens. The dose-response is not monotonic, likely because small numbers make the calculations unstable, but clearly the greatest risk is seen at the highest concentration of soluble nickel (80-fold increase in risk). Increased risk of lung cancer was also found in workers in another cohort exposed to soluble nickel; in contrast, individuals in two studies of electrolysis workers with little exposure to soluble nickel had no excess risk of lung cancer (all studies cited in Andersen et al., 1996, p 712). These results from epidemiological studies are fully consistent with the understanding provided by animal and *in vitro* studies regarding the role of nickel solubility in carcinogenesis.

Two recent epidemiological studies involving Norwegian workers have been published in the American Journal of Epidemiology (Grimsrud et al., 2002) and the Journal of Environmental Monitoring (Grimsrud et al., 2003). Neither of these articles was available when the 10th RoC was being reviewed. They are mentioned here because they are a step forward in addressing the methodological considerations you mentioned -- i.e., confounding due to exposure to mixed nickel species and exposure to other respiratory carcinogens in the cohort. Both studies show clear dose-response for soluble nickel after adjustment for smoking and also after controlling for exposure to other forms of nickel.

Both studies show that soluble nickel is a human carcinogen. In summary, no changes are needed in the information provided by the 10th RoC in summarizing the carcinogenicity of soluble nickel. However, in describing the study by Andersen et al. (1996), the word "alone" will be deleted in the next RoC.

**Item 5**:
Your fifth point states "that the 10th RoC unjustifiably indicates that nickel exposure has 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 et al., 1991), although subjects in these studies also were exposed to the known carcinogen chromium, which complicates the results.'" You note 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." You further point out that "Simonato et al. (1991) found that excess lung cancer mortality was *not* associated with cumulative exposure in nickel." You thus maintain that "the 10th RoC's suggestion that the study of mild steel welders by Simonato et al. (1991) indicates a nickel-related cancer risk is inaccurate."

Response: Simonato et al. (1991) found an increase in lung cancer risk in both mild steel and stainless steel welders. Risk was related to duration of employment and time since first employment in both types of welders. Estimation of risk associated with cumulative exposure to nickel or chromium VI was performed only for stainless steel welders; no increase in risk was found for greater exposure to either agent. Since there is abundant evidence that chromium VI is a carcinogen, a possible explanation for these results is that estimates of cumulative exposure were not accurate. In epidemiological studies where exposure is estimated from plant records, some exposed individuals may be incorrectly classified as unexposed, and vice versa. The resulting misclassification will generally make it more difficult to identify an effect. It is also possible that cumulative exposure is not the relevant exposure metric. The NTP did, however, take care to qualify its statement by mentioning that co-exposure with another carcinogen complicated the interpretation.

Next is the issue that mild steel "is almost completely devoid of nickel." Certainly there does appear to be some confusion on this issue. According to the dictionary (http://www.thefreedictionary.com/steel), mild steel is steel with less than 0.15% carbon. The "Key-to-Steel" web page (www.key-to-steel.com/articles/art85.htm) defines it as: "Mild (low-carbon) steels are normally considered to have carbon contents up to 0.25% C with about 0.4 to 0.7% Mn, 0.1 to 0.5% Si and some residuals of sulfur, phosphorus, and other elements."

There are sites on the web that identify different grades of "low carbon steel" (i.e., mild steel) as containing up to 18% nickel (www.matweb.com/search/SpecificMaterial.asp?bassnum+M1820A).

A recent paper in the Journal of Toxicology and Environmental Health, Part A (Antonini et al., 2003) discusses welding fumes from mild and stainless steels and indicates that

mild steel welding fumes do not contain nickel (at least, it was not reported to be in mild steel welding fumes). The authors state that "SS (stainless steel) welding fumes pose a greater risk to the respiratory health of welders as compared to MS (mild steel) fumes. This may be due to the presence of potentially toxic metals (e.g., chromium and nickel) present in the SS fume." Clearly in this study, conducted by the National Institute for Occupational Safety and Health (NIOSH), there appears to have been no detectable level of nickel in mild steel fumes. For this reason, the sentence making reference to the Simonato et al. (1991) study on mild steel welders in the 10th RoC will be removed.

**Item 6**:
You maintain 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." You note that "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), yet no nickel-related excess respiratory cancer risks were found in any of these studies." You acknowledge that "on average, metallic nickel exposures in these studies were relatively low" although you point out that they were "far higher than those found in the ambient air ... and at least as high or higher than metallic nickel exposures found in occupational settings today." You also mention studies in nickel-producing workers that were negative and maintain that "In light of these studies ... it was misleading (and suggestive of bias) to describe the human studies as being 'inadequate for an evaluation.'" You further assert that "while the power 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)."

Response: Historically, it has been extremely difficult to prove a negative, i.e., that metallic nickel exposure is not carcinogenic in humans. Studies attempting to do so must have adequate power and exposure must be carefully documented, preferably accounting for variable levels of exposure in individual workers. You cite five studies of cancer mortality in nickel-using industry workers (Enterline and March, 1982; Cox et al., 1981; Cragle et al., 1984; Arena et al., 1998; and Moulin et al., 2000). Your point that exposure levels were low in the cited studies may, but may not, provide an explanation for their failure to detect increased risk. You also cite two studies of nickel-producing workers (Egedahl et al., 2001; ICNCM, 1990), presumably exposed to higher levels of metallic nickel. We have reviewed these studies and will briefly summarize them below.

- Enterline and Marsh (1982) studied mortality in two groups of workers: 266 who had worked in a nickel refinery and a total of 2,943 who had worked in the plant, but not in the refinery, and therefore may have been exposed primarily to metallic nickel. There were 59 deaths from respiratory cancer among nonrefinery workers. Cumulative exposure to nickel was calculated for individual workers. Only refinery workers had substantial exposure to nickel in any form. Exposure specifically to

metallic nickel was not documented. The small size of the cohort coupled with low exposure levels severely limits the power of this study to evaluate respiratory cancers. Cox et al. (1981) studied 1,925 workers in a plant manufacturing nickel alloys from metallic nickel. Overall exposures to nickel were between 0.5 and 0.9 $mg/m^3$. Most of the workers were successfully traced, but only 117 had died, 15 from lung cancer. The overall risk of lung cancer was ~1 (thus, not elevated); however, because the estimate is so imprecise statistically, due to small numbers, it is compatible with risks between half and twice normal. Nine deaths from lung cancer occurred in men with above average exposure to nickel; for these, there was a 24% increase in risk. The small size of this study gives it limited power to support a negative conclusion.

- Cragle et al. (1984) compared 814 workers exposed to metallic nickel powder to 7,552 unexposed workers. No measures documenting individual exposure were provided, other than having worked in the department using metallic nickel (median 3.8 years). Air concentrations of nickel in the department were between 0.1 and 1.0 $mg/m^3$. Overall, 137 nickel workers had died, 6 from respiratory cancer. Nickel workers had less than half normal risk of respiratory cancer. Again, the small size of this study gives it limited power to support a negative conclusion.

- Arena et al. (1998) studied over 31,000 workers from 13 nickel alloy plants. Nickel exposures in different work areas in the plants averaged from 0.006 $mg/m^3$ to 1.5 $mg/m^3$. Compared to the overall U.S. population, all workers combined had a 13% increased risk of lung cancer, based on 831 deaths. Two points are made regarding the Arena et al. (1998) study: (1) The study may have been unable to show a dose-response because overall exposures were low, so there may have been no examples with high exposure; this possibility can not be directly evaluated because no data on dose-response are presented in the paper, and (2) the negative overall analyses combined workers with low and high exposure. If risk is increased only in workers with high exposure, this may not be evident when workers with both low and high exposure are combined.

  No data on actual exposure levels in lung cancer cases are provided in the Arena et al. study; only general exposure data for the cohort as a whole were given. Also, the only results presented are from overall analyses of the entire cohort, which included individuals from departments with a wide range of average ambient air exposures, 0.006 to 0.298 $mg/m^3$. It should be noted that the study did find a statistically significant increase in lung cancer risk [1.13 (95% CI 1.05-1.21)] using the U.S. population for comparison. The authors chose to emphasize the negative results based on a comparison with the local population, but whether this is a better comparison than the U.S. is a matter of opinion. The local population may be more similar to the study population, theoretically reducing confounding, but they may also have more exposures in common with the study population, either from the factory in question or other sources.

- Moulin et al. (2000) studied workers involved in production of stainless steel. The cohort experienced 649 deaths including 54 from lung cancer. The lung cancer

deaths were evaluated in a nested case-control study, together with 162 age- and sex-matched living controls from the cohort. Exposures to nickel and/or chromium were evaluated together for individual workers using job histories and a job-exposure matrix. No specific information on exposure to metallic nickel was presented. No association with lung cancer was found for the combined exposure, considering any of four indicators of dose.

- Egedahl et al. (2001) studied workers at a hydrometallurgical nickel refinery and fertilizer complex. Exposure was defined as ever exposed to nickel; no quantitative information on exposure of individual workers was provided. The cohort experienced 183 deaths, including 23 from respiratory cancer. The subcohort exposed to nickel experienced 59 deaths, including 7 from respiratory cancer. There were fewer deaths than expected from respiratory cancer in both the whole cohort and the nickel-exposed subgroup. This study is limited by its small size and the lack of information on levels of metallic nickel exposure in individual workers. Further, both the entire cohort and the nickel-exposed subcohort had a large deficit of deaths overall, deaths from all neoplasms, and deaths from nonmalignant respiratory disease, as well as deaths from respiratory cancers. This deficit suggests that the study may have experienced some methodological problems, for example, inadequate ascertainment of deaths or an inappropriate comparison group.

- The ICNCM study (1990) is a combined analysis of data from several cohorts. Workers in only one of these cohorts, reported by Cragle et al. (1984) and described above, were exposed to metallic nickel alone. This study included only 38 cancer deaths and only 9 lung cancer deaths and has insufficient power to demonstrate absence of excess risk. The ICNCM study also evaluated the effect of metallic nickel in combination with exposure to other forms of nickel and found no evidence of a relationship between exposure to metallic nickel and lung cancer risk (p 73).

In summary, these studies do not provide strong evidence that metallic nickel is not a human carcinogen. The lack of internal exposure-response analyses is an important weakness in all of these studies. The Cox et al. (1981) and Cragle et al. (1984) studies have insufficient power; the Enterline and Marsh (1982) and Egedahl et al. (2001) studies are limited by small size and low exposure levels; and the Moulin et al. (2000) study provides no information on exposure specifically to metallic nickel. The Arena et al. (1998) study and the analyses presented by ICNCM are potentially the most useful. One could maintain that although the power of the individual studies to evaluate the carcinogenicity of metallic nickel is limited, together they provide a consistent set of findings. However, consistency in this case may mean only that underpowered studies of populations with low exposure are unable to detect an effect. As for the point that the large size of the Arena et al. (1998) study bolsters its findings, it cannot by itself prove a negative; potential problems with this study are discussed above. Correctly, these studies "do not indicate that inhalation exposure to metallic nickel in the workplace creates an increased risk of respiratory cancer." However, they also, for the reasons stated above, fail to prove that there is no increase in risk.

IARC (1990) described the evidence regarding the carcinogenicity of metallic nickel and nickel alloys as "inadequate." Although several studies have been published since the IARC evaluation (Arena et al., 1998; Moulin et al., 2000; Egedahl et al., 2001), they do not provide enough evidence to alter this assessment. The RoC makes clear that metallic nickel is *reasonably anticipated to be a human carcinogen,* based on sufficient evidence of carcinogenicity from studies in experimental animals. The available evidence from human studies does not provide enough information either to support or contradict this evaluation, i.e., the evidence is inadequate.

As for the ACGIH classification of metallic nickel, we have looked at their most recent profile on nickel, which is from 2001. Under human studies, they cite many of the same studies mentioned above. They voice a number of reservations, including "The studies were variable in design and length of follow-up. For most, the sizes of the cohorts were relatively small. Few provided exposure data...." They conclude with the quote "... in the absence of detailed dose-response relationships and thresholds, exposure levels should be kept as low as reasonably achievable."

Although, these studies are not definitive, it may be somewhat confusing to say that the human studies are "inadequate for evaluation." Therefore, NTP will provide clarification of this phrase.

**Item 7**:
The final issue you raise is that "the 10th RoC fails to comply with the science quality principles established by Congress in the Safe Drinking Water Act Amendments (SDWA) of 1996 B 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."

Response: The OMB Guidelines assert that "[w]ith regard to analysis of risks to human health, safety and the environment maintained or disseminated by the agencies, agencies shall either adopt or adapt the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (42 U.S.C.300g-1(b)(3)(A)&(B)."[1] However, please be aware that the RoC does not deal with "analysis of risks to human health, safety and the environment" and therefore is not subject to the SDWA. As explained in the NIH Guidelines, the "NIH does not have a mandate to conduct formal risk assessments."[2] That said, the NTP does meet the many principles of the SDWA and follows NIH guidance to use "[t]he best available science and supporting studies, particularly peer-reviewed studies, conducted in accordance with sound and objective scientific practices" in preparing the RoC.[3] Certainly, the RoC process complies with its own legislative authority and is consistent with the principles of

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[1]OMB Guidelines 67 Fed. Reg. at 8458, Section V.C.

[2]NIH Guidelines at Section V.2.d.

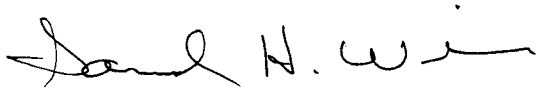
[3]NIH Guidelines at Section V.2.d and Section VII.

the Safe Drinking Water Act Amendments. Listing of nickel in the 10th RoC, as with other compounds, is based on a process of scientific review, including review by independent, non-government scientists. The review process includes several phases of scientific peer review and opportunities for public comment. Many concerns presented in this appeal were also provided by the Nickel industry during the review process as public comment and that the information, as available, was provided to the review panels for their consideration, as was information submitted by other parties as part of the review process. The review groups were provided all relevant data, including information supplied by the Nickel industry, for their consideration in reviewing Nickel Compounds and Metallic Nickel for listing in the RoC. The profiles for Nickel Compounds and Metallic Nickel are accurate summaries of the scientific evidence supporting the listings.

*Summary:* The 10th RoC complies with NIH Guidelines and the Data Quality Act in its discussions of Nickel Compounds and Metallic Nickel. Our finding is based on a complete review of this case and the following key points: (1) the NTP presented the scientific information on Nickel Compounds and Metallic Nickel in a manner consistent with the recommendations made by all review groups, (2) the information in the profile follows the format and protocol used in developing the RoC, (3) the listing complies with the "objectivity" requirement of the NIH Guidelines, and (4) the review of Nickel Compounds and Metallic Nickel was rigorous and used all available science. However, the following clarifications and deletions will be made in the next edition of the RoC: the reference to mild steel welders will be deleted; the word "alone" ['soluble nickel *alone*'] in the description of the Andersen et al. (1996) study will be deleted; the phrase "inadequate for evaluation" in the last sentence of the section, *Metallic Nickel* will be clarified; and a more detailed statement will be developed about the lack of nickel studies done in animals via oral or dermal exposure routes.

Thank you for bringing to our attention your concerns about possible inaccuracies or misinterpretations in the 10th RoC section on nickel and nickel compounds. The input of industry is critical to enabling the RoC to serve the public health interest, and we appreciate your correspondence very much.

Sincerely,



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Deputy Director