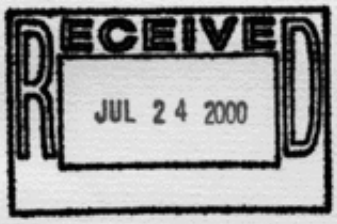
NiPERA INC.
Nickel Producers Environmental Research Association



July 21, 2000

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

Dear Dr. Jameson:

I am enclosing Comments of the Nickel Producers Environmental Research Association (NiPERA) and the Nickel Development Institute (NiDI) on the possible listing of **Soluble Nickel Compounds** in the 10th Report on Carcinogens (RoC). NTP considered the listing of all nickel compounds in the 9th RoC but deferred the listing decision until the following RoC cycle. Although both NiPERA and NiDI submitted comments on this issue in 1998, we are taking this opportunity to bring to the attention of the various RoC review bodies new information relevant to the listing decision for soluble nickel that has become available since that time.

In particular, a comprehensive evaluation of the potential carcinogenicity of soluble nickel salts was completed in March 1999 by a group of experts assembled by Toxicology Excellence for Risk Assessment (TERA) under the joint sponsorship of U.S. EPA. Health Canada, and the Metal Finishing Association of Southern California. TERA's conclusion is that the *carcinogenicity of soluble nickel salts via inhalation and oral exposure cannot be determined.*

NiPERA submitted TERA's *Toxicological Review of Soluble Nickel Salts* to the NTP Director in April 1999. But RG1, RG2, and the Board of Scientific Counselors RoC Subcommittee had concluded their 9th RoC deliberations before then; accordingly, they did not have the benefit of the TERA Review. With nickel compounds having been deferred until the 10th RoC, those groups will now have an opportunity to consider the TERA Review. Moreover, two review articles based on the TERA work (Haber *et al.,* 2000a & 2000b) have recently been published in *Regulatory Toxicology and Pharmacology* (enclosed). We believe that the members of RG1, RG2, and the Board of Scientific Counselors RoC Subcommittee need to have the opportunity to evaluate these reports before any decisions are made about listing Soluble Nickel Compounds in the 10th RoC.

I am also enclosing information relating to an on-going short-term inhalation study of nickel sulfate hexahydrate and nickel subsulfide in rats that is being sponsored by NiPERA. This information confirms that the maximum tolerated dose for rats was used in the NTP's earlier inhalation bioassay of nickel sulfate hexahydrate.

Finally, the attached Comments summarize the most relevant data sets for soluble nickel compounds. These data indicate that at concentrations high enough to cause chronic lung toxicity/cell proliferation, soluble nickel compounds may enhance the respiratory carcinogenicity of other inhaled carcinogenic agents (*e.g.,* cigarette smoke, nickel subsulfide), but that they do

2605 Meridian Parkway, Suite 200, Durham, NC 27713
Telephone 1-919-544-7722 • Fax 1-919-544-7724

not appear to induce respiratory cancer by themselves. We believe the data—when considered in a weight-of-the-evidence evaluation—show that **Soluble Nickel compounds** should not be identified either as "*known*" or as "*reasonably anticipated*" human carcinogens.

We look forward to interacting with NTP on this issue. If you have any questions about the enclosed comments, please contact me.

Sincerely,

[redacted]

Adriana R. Oller, Ph.D., DABT
Director of Research

Enclosure

Comments of the Nickel Producers Environmental Research Association and the Nickel Development Institute Regarding the Potential Listing of Water Soluble Nickel Compounds in the 10th Report on Carcinogens

1. Introduction

These Comments are being submitted by the Nickel Producers Environmental Research Association (NiPERA) and the Nickel Development Institute (NiDI) for consideration by the relevant NTP review bodies as they formulate recommendations regarding the possible listing of water soluble nickel compounds in the 10th Report on Carcinogens (RoC).

During its deliberations on the 9th RoC, NTP initially considered listing *Nickel and All Nickel Compounds* as "*known human carcinogens*" but decided to focus solely on the listing of nickel compounds, putting metallic nickel off until the 10th RoC. Ultimately, the decision on listing nickel compounds also was deferred until the 10th RoC, so that nickel metal, nickel alloys, and the various nickel compounds could be addressed at one time.

In 1998, NiPERA submitted two sets of comments (dated October 13, 1998 and November 20, 1998) on NTP's proposal to list *All Nickel Compounds* as "*known human carcinogens.*" We pointed out that the proposal failed to recognize the critical importance of speciation in evaluating the toxicity and potential carcinogenicity of the various forms of nickel. Each compound or species of a metal, like nickel, has its own physico-chemical properties that dictate how it behaves under a given set of conditions, including interactions with biological organisms. Thus, the fact that one form of nickel may be carcinogenic via a particular route of exposure (*e.g.*, nickel subsulfide by inhalation) does not mean that a second nickel species (*e.g.*, nickel sulfate hexahydrate) also will be carcinogenic or that the first nickel species will be carcinogenic via a different route of exposure (*e.g.*, ingestion).

We focused in particular on NTP's proposal to include water soluble nickel compounds in the category of "*known human carcinogens.*" We noted that while the epidemiological studies suggest some role for soluble nickel in respiratory carcinogenesis, the data are conflicting and difficult to interpret because of substantial confounding exposures in all of the refinery studies where an increased cancer risk was found. We also pointed out that the animal studies provide no evidence of carcinogenicity of soluble nickel by relevant routes of exposure (oral or inhalation) and that mechanistic data indicate that soluble nickel is very unlikely to act as an initiator or complete carcinogen.

Subsequent to NTP's consideration of soluble nickel compounds in 1998, a new comprehensive evaluation of the potential carcinogenicity of soluble nickel salts has become available. This evaluation was performed by an independent scientific organization, Toxicology Excellence for Risk Assessment (TERA), under the joint sponsorship of U.S. EPA, Health Canada, and the Metal Finishing Association of Southern California. The TERA evaluation provides a very thorough and well balanced analysis of the available data associated with soluble nickel compounds. TERA's evaluation was independently reviewed by a panel of experts convened by ITER (International Toxicity Estimates for Risk) in deliberations that lasted two days and included representatives from academia (4 people), regulatory agencies (4 people), and industry (1 person). This extensive peer-review process included the consideration of detailed public comments, thereby

providing a unique opportunity to utilize the diverse expertise of the panel in achieving the most reasonable interpretation of the available animal, human, and mechanistic data. Following the peer review deliberations, TERA revised its report and released it in March 1999. TERA's conclusion, as discussed more fully below, was that the *carcinogenicity of soluble nickel salts via inhalation and oral exposure cannot be determined.*

NiPERA submitted TERA's *Toxicological Review of Soluble Nickel Salts* to the NTP Director in April 1999. By that time, however, RG1, RG2, and the Board of Scientific Counselors RoC Subcommittee had already completed their review of nickel compounds for purposes of the 9th RoC reporting cycle. Consequently, neither RG1, nor RG2, nor the Board of Scientific Counselors RoC Subcommittee had the benefit of TERA's comprehensive and well-balanced Review when they considered the potential carcinogenicity of soluble nickel compounds.

Since a listing decision on nickel compounds has been deferred until the 10th RoC, there is a new opportunity for RG1, RG2, and the Board of Scientific Counselors RoC Subcommittee to consider the TERA Review. Moreover, an abbreviated version of TERA's work has now been published as a two-part review article in *Regulatory Toxicology and Pharmacology* (Haber et al. 2000a & 2000b). Copies of those articles are enclosed with these Comments. We believe that the TERA Review will help persuade the members of RG1, RG2, and the Board of Scientific Counselors RoC Subcommittee that the 9th RoC proposal to include soluble nickel on the list of "*known human carcinogens*" is not scientifically justified.

We also are attaching to these Comments information relating to an on-going short-term inhalation study of nickel sulfate hexahydrate and nickel subsulfide in rats that is being sponsored by NiPERA. As explained below, early mortality results from that study confirm that the maximum tolerated dose for rats was used in the earlier NTP inhalation bioassay, which found no evidence for the carcinogenicity of nickel sulfate hexahydrate in rats or mice.

In the balance of these Comments, we summarize the most relevant data sets for soluble nickel compounds. These data indicate that at concentrations high enough to cause chronic lung toxicity/cell proliferation, soluble nickel compounds may enhance the respiratory carcinogenicity of other inhaled carcinogenic agents (*e.g.,* cigarette smoke, nickel subsulfide), but that they do not appear to induce respiratory cancer by themselves. We believe the data—when considered in a weight-of-the-evidence evaluation—show that soluble nickel compounds should not be identified either as "*known*" or as "*reasonably anticipated*" human carcinogens.

2. Human Data

Epidemiologic data from nickel workers are difficult to interpret because of mixed exposures that include not only different nickel compounds but also other inorganic compounds (*e.g.,* arsenic, cobalt, strong acid mists) and organic combustion products (ICNCM, 1990). In addition, the confounding effects of cigarette smoking on respiratory cancers have almost never been adequately considered. With regard to exposures to soluble nickel compounds, a comparison of electrolysis workers at Port Colborne, Canada with those at Kristiansand, Norway reveals a disparity in respiratory cancer risk, with excess lung cancers occurring only in Kristiansand workers. Because of differences in processes, the Kristiansand workers are believed to have been exposed to similar levels of soluble nickel but they also handled approximately seven times more insoluble nickel (per unit of soluble nickel) than workers at

Port Colborne. In addition, in the estimation of Kristiansand exposures, basic nickel carbonate (water insoluble) was included in the soluble compounds category, while it was classified as insoluble at Port Colborne. In another cohort of hydro-metallurgical workers at Clydach who had high cumulative exposure to soluble forms of nickel but low exposures to oxidic and sulfidic forms of nickel, there was no evidence of increased risks of respiratory cancer. From these studies, the ICNCM Report concluded that, while there was evidence that soluble nickel exposure ($\geq$ 1 mg Ni/m^3) could increase the risk of respiratory cancers, the effect might be one of enhancing risks associated with co-exposure to less soluble forms of nickel or other non-nickel compounds.

In a 1998 study of Finnish refinery workers exposed predominantly to soluble nickel, three nasal cancer cases were identified and a 2-fold increase in lung cancer risk was found in nickel workers with more than 20 years employment (Anttila et al., 1998). Unfortunately, smoking data are unavailable for these workers. And, as far as the observed nasal cancers are concerned, even though the Finnish workers were predominantly exposed to soluble nickel during their employment at the refinery, their previous job experiences (*e.g.,* carpentry), as well as concomitant exposures to insoluble nickel compounds and acid mists, make the establishment of a causal association with soluble nickel compounds impossible.

A 1996 study of the Kristiansand cohort updated cancer morbidity and reported newly available information on the smoking characteristics of the workers (Andersen et al., 1996). A synergistic lung cancer response between smoking and exposure to a mixture of soluble and insoluble nickel compounds was observed. In the small number of nickel-exposed workers who did not smoke, there was no evidence that nickel exposure increased the risk for lung cancer. These results can be interpreted as providing supportive evidence for the possible role of soluble nickel as an enhancer of carcinogenicity, rather than as an initiator or complete carcinogen. Thus, although suggestive of some kind of association, the Finnish and Kristiansand cohorts do not demonstrate that exposures to soluble nickel, in the absence of exposures to known or suspected carcinogens, resulted in increased respiratory cancer risks.

The combined, integrated information from all studies strongly suggests that soluble nickel behaves differently from sulfidic and oxidic nickel; soluble nickel appears to increase respiratory cancer risks **only** in the presence of relatively high concentrations of insoluble forms of nickel or cigarette smoking. In the only study of nickel workers exposed solely to soluble nickel compounds, no excess respiratory cancers were noted. Even though this study involved a relatively small population of nickel platers (284 workers), with exposure levels estimated between 0.01-0.08 mg Ni/m^3, and mean exposure of ~3 years (median ~1 year), the cohort had >30 years of follow up (Pang *et al.,* 1996; Sorahan *et al.* 1987). These results are consistent with those of the ICNCM Report, Andersen *et al.,* 1996 and Anttila *et al.,* 1998, and indicate, at most, an enhancing rather than a direct acting role (as initiator or complete carcinogen) for soluble nickel in respiratory carcinogenesis.

The ICNCM report recognized the limitations of human studies involving mixed exposures and pointed out the importance of mechanistic data and the results of the animal carcinogenesis studies (using inhalation as the route of exposure) to help understand the human health risks associated with the individual nickel compounds. In its concluding remarks, the ICNCM stated:

"In addition, future work that improves our understanding of the mechanisms of nickel carcinogenesis may help to unify and explain the results of our findings in conjunction with those provided by the animal experimentation."

As discussed below, the animal studies and mechanistic data indicate strongly that soluble nickel salts by themselves are not carcinogenic.

3. Animal Data

In 1996, NTP completed a two-year carcinogenicity study of nickel sulfate hexahydrate in rats and mice. This study showed no increases in respiratory tumors for male or female rats and mice, inhaling nickel sulfate hexahydrate at concentrations up to 0.5 mg/m^3 (0.1 mg Ni/m^3) for rats and 1.0 mg/m^3 (0.2 mg Ni/m^3) for mice. By contrast, inhalation of nickel subsulfide at the same concentration (0.1 mg Ni/m^3) resulted in increased combined lung adenoma/carcinomas in rats. These results clearly demonstrated that the chemical form of nickel (water soluble nickel sulfate versus sparingly soluble crystalline nickel subsulfide) impacted the bioavailability of the nickel ion at target nuclear sites and the induction of tumors.

Interestingly, soluble nickel compounds appear to be toxic to the lung at lower concentrations than more insoluble nickel compounds. This would be expected due to the higher (if transient) levels of nickel ions at the lung surface that will be present upon inhalation of soluble nickel compounds. Nickel ions bind avidly to proteins causing inflammation and toxicity. It is the increased toxicity of soluble nickel compounds that prevented NTP from testing nickel sulfate hexahydrate at concentrations higher than 0.5 mg/m^3.

The relevancy of the NTP studies to evaluate human cancer risk has been questioned by some people on two grounds: First, it has been suggested that the maximum tolerated dose (MTD) was not reached in the NTP two-year bioassay and that concentrations higher than 0.5 mg/m^3 of nickel sulfate hexahydrate should have been tested. Second, the exposure levels of the animals in the NTP study were said to be lower than those experienced by occupational cohorts. Neither of these concerns is valid.

As to the first point, a short-term inhalation study of nickel sulfate hexahydrate and nickel subsulfide in rats that is currently being sponsored by NiPERA has confirmed that a higher dose (than 0.5 mg/m^3) would have resulted in an unacceptable level of toxicity-based mortality. This study is being conducted by J. Benson at Lovelace Research Institute and was designed with input from G. Oberdörster (Rochester University), and J. Everitt (CIIT) following suggestions made by Drs. R. Marenpot, R. Herbert and D. Dixon of NIEHS. J. Benson is the same investigator who conducted the cancer bioassay for NTP. The protocol for this study can be found in Appendix 1 to these comments. The goals of this study are to: (i) understand the relationship between the induction of inflammation and lung epithelial cell proliferation for nickel subsulfide and soluble nickel sulfate hexahydrate; (ii) gather quantitative epithelial cell proliferation data that can be incorporated into a biologically-based risk assessment model; (iii) measure several endpoints in lung tissue to learn about the genotoxic mechanisms that may be involved in the induction of rat lung tumors by nickel subsulfide; and (iv) understand the relationship between the induction of inflammation and genotoxic effects for the two nickel compounds.

The original design of the study included exposure of rats to nickel sulfate hexahydrate at 0.03, 0.1, and 0.4 mg Ni/m^3 for 13-weeks (a much shorter exposure than the 2 years of the NTP bioassay). However, early into the study, an adjustment to the nickel sulfate concentrations had to be made because 10/39 rats (25%) exposed to the highest concentration of nickel sulfate hexahydrate (2 mg/m^3, 0.4 mg Ni/m^3) died during the second week of exposure. The highest concentration was then reduced to 1 mg/m^3 (0.2 mg Ni/m^3), and new animals were added to the study. These toxicity results indicate that for a two year study (rather than a 13-week exposure period) a concentration below 1 mg/m^3 (0.2 mg Ni/m^3) would need to be selected. This confirms that the 0.5 mg/m^3 (0.1 mg Ni/m^3) exposure level used in the two-year NTP bioassay was indeed at or near the maximum tolerated dose (or minimum toxicity dose). It also indicates a steep dose-response curve for respiratory toxicity from nickel sulfate. A first draft report on the results from the short-term inhalation study will be available by the end of 2000. Further discussion of the NTP bioassay study design and results (including selection of the MTD) can be found in the TERA 1999 Report (pages 65-66) and in Haber et al. (2000a, pages 219-220).

As to the second point, at the NTP BSC Report on Carcinogens Subcommittee meeting in December 1998, one reviewer noted that the highest concentration to which rats were exposed in the NTP bioassay was 0.1 mg Ni/m^3 while workers in some of the cohorts studied by the ICNCM experienced soluble nickel exposures $\geq$ 1 mg Ni/m^3. The reviewer suggested that the differences in exposure levels could explain why rats did not get tumors while some workers did. In considering this point, it is important to note that the aerosol used in the NTP studies was carefully prepared to have a narrow range of particle sizes with a mass median aerodynamic diameter (MMAD) of 2-3 µm. In contrast, the particle size distribution of the aerosols in the workplace is broader and characterized by coarser particles (*e.g.,* MMAD> 50 µm). Particles in the 2-3 µm range comprise less than 10% of the workplace total. Therefore to do a proper comparison (apples to apples) between animal and human exposures, the particle size of the aerosols must be taken into consideration. Preliminary results from an animal to human extrapolation study based on deposition/clearance models for rat and human lungs, indicate that after accounting for particle size distribution, the exposures experienced by the rats in the NTP studies appear equivalent (in terms of nickel lung burden) to those experienced by workers in the nickel refinery epidemiological studies (Hsieh et al., 1999a, b, and c). See also the further discussion of this issue in the TERA 1999 Report (pages 45 and 66) and in Haber et al. (2000a, page 220).

4. Mechanistic Data

Models for nickel-mediated induction of respiratory tumors suggest that the main determinant of the respiratory carcinogenicity of a nickel species is likely to be the bioavailability of the Ni (II) ion at nuclear sites of target epithelial cells (Costa, 1991; Oller *et al.*, 1997; Haber *et al.,* 2000a). Only those nickel compounds that result in sufficient amounts of bioavailable nickel ions at nuclear sites of target cells (after inhalation) will be respiratory carcinogens.

The factors that will influence Ni (II) ion bioavailability in epithelial cells of the lung are: presence of particles on bronchio-alveolar surface, mechanism of lung clearance (dependent on solubility), mechanism of cellular uptake (dependent on particle size, particle surface area, particle charge), and intracellular release rates of Ni (II) ion. Those nickel compounds that are: (1) insoluble enough to allow accumulation of particles at the cell surface, (2) have an

intermediate lung clearance rate that allows them to persist in the lung, (3) have a high uptake of particles into epithelial cells via phagocytosis, and (4) have increased release rates of Ni (II) ion inside the cells, will result in greater accumulation of Ni (II) ion at nuclear target sites. Inhalable size particles of nickel subsulfide represent a good example of a high Ni (II) bioavailable dust for respiratory carcinogenesis.

By contrast, water soluble nickel compounds will not be present as particles on the cell surface (rather there will be Ni (II) ions and counter ions), will experience rapid clearance from the lung (decreasing the availability of Ni (II) ions for transport into the cell), will have inefficient transport into the cells through the cell membrane (*e.g.,* magnesium channels, Hausinger, 1992), and will avidly bind to proteins inside and out of the cells (Harnett *et al.,* 1982). The end result is that inhalation of soluble nickel compounds leads to very low bioavailability of Ni (II) ions at nuclear target sites of lung epithelial cells.

Only inhalation studies can be used to evaluate the interaction of all the above mentioned factors that determine Ni (II) ion bioavailability at target sites. The NTP animal studies (NTP 1996 a,b,c) are consistent with the *nickel ion bioavailability theory* described above.

The Haber *et al.* (2000a) paper (pages 220-224) discusses mode of action and suggests that perhaps soluble nickel compounds have a different mode of action at low (non carcinogenic) and high (carcinogenic) doses. This is a theoretical possibility that is consistent with the model described above. *In vivo,* however, the high concentrations of soluble nickel compounds needed to induce tumors (rather than simply to promote cell proliferation) are unlikely to be reached because humans or animals would die from respiratory toxicity before high enough levels are achieved at target nuclear sites. The animal and human data discussed above provide evidence to support this contention.

Another question that needs to be considered is how soluble nickel compounds can be positive in *in vitro* studies and negative in the inhalation animal studies. In general, studies of genotoxicity in bacteria or cultured cells have indicated that nickel compounds can induce chromosomal aberrations and cellular transformation but not gene mutations. All nickel compounds have the ability to induce these effects albeit at different concentrations. Soluble nickel compounds require higher concentrations than particulate nickel compounds to produce the same effects. The lower genotoxic potency of soluble nickel compounds is attributed to the ineffective cellular uptake of the nickel ion from soluble nickel compounds compared to the effective phagocytosis mechanism for more insoluble nickel compounds. The *in vitro* data can be reconciled with the negative animal data because *in vitro* studies do not account for organ clearance. Therefore, if concentrations of soluble nickel are high enough in the Petri dish, given enough time, some nickel ions will eventually reach the nucleus of the cells. *In vivo,* this is not the case. The inefficient cellular uptake of nickel ions is complemented by the rapid clearance of soluble nickel compounds. Because of the toxicity of soluble nickel compounds, exposed animals are likely to die before a high enough concentration of nickel ions (*i.e.,* the concentration needed to induce tumors) can be reached in the nucleus of respiratory target cells.

5. Weight-of-the-Evidence Determination for Soluble Nickel Compounds.

The combined, integrated information from human, animal and mechanistic studies strongly suggests that soluble nickel behaves differently from sulfidic and oxidic nickel with regard to carcinogenicity. Therefore, regulatory and classification decisions for water soluble nickel should be made separately from decisions regarding the less soluble forms of nickel.

Under NTP's revised criteria, a substance may be listed as "*Known To Be a Human Carcinogen*" when:

> "[t]here is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer." See NTP, 9th Report on Carcinogens, page I-2.

A substance may be listed as "*Reasonably Anticipated To Be a Human Carcinogen*" when:

> "There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or
>
> there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset." See NTP, 9th Report on Carcinogens, page I-2.

The criteria go on to state:

> "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance." See NTP, 9th Report on Carcinogens, page I-2.

It is clear from these criteria that the NTP intends to apply a weight-of-evidence approach in reaching a decision whether to list a compound as "*known*" or "*reasonably anticipated*" to be a human carcinogen. A weight-of-evidence approach to the nickel data (as used by TERA), indicates that soluble nickel should not be listed as "*reasonably anticipated*" to be a human carcinogen, let alone labeled as a "*known*" human carcinogen. None of the epidemiological studies of workers exposed to soluble nickel conducted to date establishes a causal relationship between inhalation (or any other) exposures to soluble nickel compounds and increased respiratory cancer risks. As noted by others (ICNCM 1990, TERA 1999, Mauderly 1997), human evidence that soluble nickel is related to respiratory cancer is limited to workplaces in which exposures to soluble nickel were highly confounded with exposure to known or likely

carcinogens. In instances where exposures were to soluble nickel without substantial amounts of less soluble compounds (which have been found to be carcinogenic in NTP's inhalation bioassays), there has been no evidence of excess respiratory cancer risk (Port Colborne electrolysis department, Clydach hydrometallurgical workers, British elecotroplating workers). Furthermore, there is no evidence for the carcinogenicity of soluble nickel via inhalation, ingestion, or dermal exposure in animals. And, from a mechanistic perspective, inhalation of soluble nickel is not expected to result in any significant bioavailability of Ni (II) ions at the target nuclear sites. The human data—supplemented by the animal studies and mechanistic data—suggest that soluble nickel exposures may enhance cancer risks only in the presence of concomitant exposures to other respiratory carcinogens and only when present at concentrations high enough to cause chronic toxicity/cell proliferation.

This leaves only two animal studies, involving a non-relevant route of exposure (intraperitoneal injection[1]), as a possible basis for listing soluble nickel in the 10th RoC. While tumorigenic responses were observed in these studies, they must be considered in light of the weight of evidence from a dozen or so negative studies of soluble nickel in animals, including NTP's own inhalation bioassay. In NiPERA's submission to NTP of November 20, 1998, extensive comments were presented regarding the shortcomings of these two intraperitoneal studies. We continue to stand by those comments. Furthermore, inasmuch as tumorigenic responses in these studies were seen only in one species (rat), the results would not meet the criteria for listing soluble nickel compounds as *"reasonably anticipated to be a human carcinogen"* even if there were not significant shortcomings in the studies.

In sum, based on a weight-of-the-evidence evaluation, water soluble nickel compounds by themselves cannot "reasonably be anticipated to be a human carcinogen" by any relevant route of exposure. As the authors of the TERA Report concluded:

> "The carcinogenic potential of inhalation exposure to soluble nickel c*annot be determined* because the existing evidence is composed of *conflicting* data." Haber et al. 2000a (p. 224).
>
> "The carcinogenic potential of oral exposure to soluble nickel *cannot be determined* because there are *inadequate data* to perform an assessment." Haber et al. 2000b (p. 236).

Moreover, as Mauderly (1997) points out, if soluble nickel compounds were carcinogenic to humans, it would be "*the only known case of a declared human carcinogen that was negative in rats and mice in a well-conducted inhalation bioassay.*"

Water soluble nickel compounds, therefore, should not be included on the list of substances that are *"reasonably anticipated to be a human carcinogen,"* and they certainly should not be included on the list of *"known human carcinogens."* Keeping soluble nickel off these lists would be consistent with the determinations that have been made by other organizations in recent years. For example, the European Union gave nickel sulfate hexahydrate a carcinogen category

---

[1] Kasprzak et al., 1990; Diwan et al., 1992.

3 classification[2]; ACGIH assigned water soluble nickel compounds a category 4 classification[3]; and, as noted above, TERA concluded that the carcinogenic potential of soluble nickel salts *cannot be determined*. In each of these cases the assessment concluded that the data are insufficient to establish the equivalent of a *"known"* or *"reasonably anticipated"* carcinogenic classification for water soluble nickel compounds.[4] There is no sound scientific basis for NTP to reach a different conclusion.

---

[2] EU Carcinogen Category 3: *"Cause concern for man owing to possible carcinogenic effects, but in respect of which the available information is not adequate for making a satisfactory assessment."*

[3] ACGIH Category 4. "Not classifiable as a human carcinogen."

[4] To prevent the possibility that exposure to soluble nickel in the workplace may enhance the carcinogenic effects of smoking or exposure to other carcinogenic agents, occupational exposures to soluble nickel should be maintained below the level that may cause chronic respiratory inflammation. An Occupational Exposure Level of 0.1 mg Ni/m^3 for inhalable soluble nickel compounds, as recommended by ACGIH, should be adequately protective even in situations involving mixed exposures.

Table 1: Respiratory Cancer Risk Relative to Occupational Nickel Exposure

Cohort	Number of Workers	Lung Cancer SMR	Nasal Cancer SMR (# of deaths)	Nickel Species	Typical Exposure Concentrations In mg Ni/m³ (Median Values)
"High" Exposure and/or "High" Risk Cohorts					
Clydach, Wales refinery before 1930 (ICNCM 1990)	1,348	394***	2,114*** (74)	Sulfidic, Oxidic, Soluble, Metallic	>10, >10, >1, >0.5
INCO, Ontario sintering (ICNCM 1990, Roberts *et al.*, 1989)	3,769	261***	5,073 *** (25)	Sulfidic, Oxidic, Soluble, Metallic	>10, >10, >1, <0.01
Kristiansand, Norway refinery[1] (ICNCM 1990, Andersen et al 1996)	4,764	320[1]***	1,800[1]*** (32)	Sulfidic, Oxidic Soluble, Metallic	>0.5, >2 >0.5, >0.5
Outokumpu refinery, Finland (Anttila et al 1998)	1,388	212**	879* (2)	Sulfidic, Soluble[5], Sulfuric acid mist	0.06-0.4, 0.3-0.8
"Low" Exposure and "Low" Risk Cohorts					
INCO, Ontario non-sintering (ICNCM 1990, Roberts *et al.*, 1989)	37,117	111*	142 (6)	Sulfidic, Oxidic Soluble	<0.5, <0.5 <0.3
Falconbridge, Ontario mining and smelting (ICNCM 1990, Shannon *et al.*, 1991)	8,374	128*	130 (1)	Sulfidic, Oxidic	0.02-0.22 (0.1) 0.01-0.05 (0.01)
High Nickel Alloys, USA (Arena et al 1998)	31,165	113* 101[2]	35[3] (3)	Oxidic, Metallic	0.01- 0.3 (0.08) <0.01; 1.5 in one department
Clydach, Wales refinery after 1930 (ICNCM 1990)	1,173	124	526 (1)	Oxidic, Sulfidic. Metallic	>5, >1, >1
Hanna, Oregon mining & smelting (Cooper & Wong, 1981)	1,510	147	0	Oxidic	<1
Oak Ridge barrier production. USA (Cragle et al 1984)	813	60	0	Metallic	<1
Huntington Alloys (ICNCM 1990; Enterline & Marsh, 1982)			232 (2)	Oxidic	0.001-0.5 (0.01)
				Metallic	0.0-0.4 (0.03)
				Sulfidic	<0.01, >3 in one department
Cohort 1	1,855	99			
Cohort 2	1,353	98			
SLN New Caledonia Mining and Smelting (Goldberg et al 1987)	79 cases 223 controls	RR=1.4[4]	0	Oxidic	<2
Wiggin Alloys, UK (Cox et al 1981)	1,907	95	0	Oxidic, Metallic	<1, <1
Sherritt Gordon refining, Alberta (Egedahl et al 1993)	715	74	0	Sulfidic, Oxidic, Metallic	<1, <1, <1
British electroplaters (Pang et al 1996)	284	125[1]	0	Soluble	0.01 - 0.08[6]

SMR Standardized Cancer Mortality Ratio

*** Significance Level ($p < 0.001$); ** Significance Level ($p < 0.01$); * Significance Level ($p < 0.05$)

1 Standardized Incidence Ratio

2 Based on local rate

3 Respiratory cancer, excluding bronchus, trachea, lung

4 Case-control study, RR = relative risk reported

5 Soluble nickel exposures from company measurements taken in 1966

6 Exposure data derived from survey of electroplaters (TERA, 1999)

6. References

American Conference of Governmental Industrial Hygienists (ACGIH). 1999. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

Andersen, A., Engeland, A.; Berge, S.R., and Norseth, T. 1996. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occup. Environ. Med., 53, 708-713.

Anttila, A., Pukkala, E., Aitio, A., Rantanen,T., and Karjalainen, S. 1998. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int. Arch. Occup. Environ. Health, 71, 245-250.

Costa 1991. Molecular mechanisms of nickel carcinogenesis. Ann. Rev. Pharmacol Toxicol. 31: 321-37.

Diwan, B. A., Kasprzak, K. S., and Rice, J. M. 1992. Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. Carcinogenesis 13(8): 1351-1357.

Haber, L. T.; Erdreicht, L.; Diamond, G. L.; Maier, A. M.; Ratney, R.; Zhao, Q.; and Dourson, M. L. 2000a. Hazard Identification and Dose Response of Inhaled Nickel-Soluble Salts. Regulatory Toxicology and Pharmacology, 31: 210-230.

Haber, L. T.; Diamond, G. L.; Zhao, Q.; Erdreicht, L.; and Dourson, M. L. 2000b. Hazard Identification and Dose Response of Ingested Nickel-Soluble Salts. Regulatory Toxicology and Pharmacology, 31: 231-241.

Harnett, P. B., Robison, S. H., Swartzendruber, D. E., Costa, M. 1982. Comparison of protein, RNA, and DNA binding and cell-cycle-specific growth inhibitory effects of nickel compounds in cultured cells. Toxicol. Appl. Pharmacol., 64: 20-30.

Hausinger, R. P. 1992. Biological utilization of nickel. In Nickel in human health: current perspectives (E. Nieboer, and J. O. Nriagu, Eds. John Wiley and Sons, Inc. New York, NY. Pages 21-36.

Hsieh, T. H.; Yu, C. P.; Oberdörster, G. 1999a. A dosimetry model of Ni compounds in the rat lung. Inhalation Toxicology, 11: 229-248.

Hsieh, T. H.; Yu, C. P.; Oberdörster, G. 1999b. Deposition and clearance models of Ni compounds in the mouse lung and comparisons with the rat models Aerosol Science and Technology, 31: 359-372.

Hsieh, T. H.; Yu, C. P.; Oberdörster, G. 1999c. Modeling of deposition and clearance of inhaled Ni compounds in the human lung. Regulatory Toxicology and Pharmacology, 30, 18-28.

ICNCM Report. 1990. Report of the International Committtee on Nickel Carcinogenesis in Man. Scand. J. Work Environ. Health 16(1): 1-82.

Kasprzak, K. S., Diwan, B. A., Konishi, N., Misra, M., and Rice, J. M. 1990. Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. Carcinogenesis, 11(4), 647-652.

NTP (National Toxicology Program) Technical Report 1996a. Toxicology and carcinogenesis studies of nickel subsulfide in F344/N rats and B6C3F$_1$ mice. NTP TR 453, NIH publication Series No. 96-3369.

NTP (National Toxicology Program) Technical Report 1996b. Toxicology and carcinogenesis studies of nickel sulfate hexahydrate in F344/N rats and B6C3F$_1$ mice. NTP TR 454, NIH publication Series No. 96-3370.

NTP (National Toxicology Program) Technical Report 1996c. Toxicology and carcinogenesis studies of nickel oxide in F344/N rats and B6C3F$_1$ mice. NTP TR 451, NIH publication Series No. 96-3363.

Oller, A. R., Costa, M., and Oberdörster, G. 1997. Carcinogenicity assessment of selected nickel compounds. Toxicol. Appl. Pharmacol., 143: 152-166.

Pang, D., Burges, D. C., and Sorahan, T. 1996. Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945-93. Occup. Environ. Med., 53, 714-717.

Sorahan, T., Burges D.C.L., Waterhouse, J. A. H. 1987. A mortality study of nickel/chromium platers. Br. J. Ind. Med. 44: 250-258.