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To: Dr. C. W. Jameson (National Toxicology Program) and Members of the NTP Board of Scientific Counselors RoC Subcommittee

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Dear Dr. Jameson and Members of the NTP Board of Scientific Counselors RoC Subcommittee:

The purpose of this letter is to request that consideration be given to several important developments that have occurred since the Board of Scientific Counselors (BSC) Subcommittee last considered a proposed carcinogen classification for **Soluble Nickel Compounds.** As some of you may recall, following a closely divided vote by RG2, the BSC Subcommittee, at its December 1998 meeting, voted to recommend that **Nickel Compounds** (soluble and insoluble) be listed as *known human carcinogens* in the 9th Report on Carcinogens (RoC). The Nickel Producers Environmental Research Association (NiPERA) opposed the recommendation to list soluble nickel compounds *as known human carcinogens*, noting that the animal data by relevant routes of exposure are negative and that there are plausible alternative explanations for the increased cancer risks seen among workers with mixed exposures to soluble nickel and other agents, including sulfidic and oxidic forms of nickel.

Earlier this year, NTP decided to defer the listing decision for **Nickel Compounds**, so that they could be considered along with **Metallic Nickel and Certain Nickel Alloys** for possible listing in the 10th RoC. That deferral creates an opportunity to consider a number of significant developments relating to soluble nickel compounds that had not yet occurred when soluble nickel was reviewed under the rubric of **Nickel Compounds** in 1998 and that, consequently, were not considered by the BSC Subcommittee or by RG1 and RG2 when the listing recommendation was voted on at that time. These include:

- The release in March 1999 of an exhaustive, peer-reviewed *Toxicological Review of Soluble Nickel Salts* prepared 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. Based on their comprehensive evaluation of all the evidence relating to the potential carcinogenicity of soluble nickel salts, and following the recommendations of the *ITER* (*International Toxicity Estimates for Risk*) peer review panel, the authors of the *TERA Review* concluded that the *carcinogenicity of soluble nickel salts via inhalation and oral exposure cannot be determined.* The *TERA Review* was sent to NTP in the spring of 1999. However, this report is not listed as a submission on the NTP Website and, of course, was not considered by RG1, RG2, or the BSC Subcommittee when those groups deliberated on the classification of soluble nickel compounds in 1998.

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- The publication earlier this year of two review articles based on the *TERA* work (Haber *et al.,* Hazard Identification and Dose Response of Inhaled Nickel-Soluble Salts. *Regulatory Toxicology and Pharmacology* 31:210-230 (2000); Haber *et al.,* Hazard Identification and Dose Response of Ingested Nickel-Soluble Salts. *Regulatory Toxicology and Pharmacology* 31:231-241 (2000).

- The availability of preliminary results from an on-going short-term inhalation study of nickel sulfate hexahydrate and nickel subsulfide in rats that is being sponsored by NiPERA (Lovelace, Dr. J. Benson). This information confirms that the maximum tolerated dose for rats was indeed reached in the NTP two year inhalation bioassay of nickel sulfate hexahydrate, a point that was questioned by some BSC Subcommittee members during deliberations at the December 1998 meeting.

The *TERA Review*, the Haber *et al.* review articles, and information regarding the short-term inhalation study at Lovelace have been furnished to NTP officials over the last 18 months. However, as noted above, this material has not been considered by RG1, RG2, or the BSC Subcommittee.

In view of the split vote at the RG2 group level due to disagreements regarding the carcinogenicity of soluble nickel, and the discussions that took place at the December 1998 meeting of the BSC Subcommittee, it is quite possible that if these groups had had the benefit of a thorough carcinogenicity review document on soluble nickel compounds such as the *TERA Review*, these groups would have reached a different conclusion regarding the carcinogenicity of soluble nickel. It is striking that only one month following the BSC Subcommittee's recommendation of a *known human carcinogen* listing for soluble nickel compounds, the *ITER* peer review panel concluded that the *carcinogenicity of soluble nickel salts cannot be determined.* We believe these disparate conclusions reflect the fact that the BSC Subcommittee was presented with a poorly written and incomplete Background Document and had only three hours to review all nickel compounds, while the *ITER* peer review panel had a very thorough, well written document and two days to focus on just soluble nickel salts.

In light of these significant new developments, NTP should reconsider the recommended carcinogen classification for **Soluble Nickel Compounds**. At the same time, it is clear that the BSC Subcommittee members will not have a chance to review the comprehensive *TERA* document and the Haber *et al.* papers before convening on December 13. Accordingly, we urge the BSC Subcommittee to request that NTP reopen the listing recommendation for **Soluble Nickel Compounds** and ensure that an opportunity exists for all the relevant groups within the RoC structure to consider these new developments before the listing of **Soluble Nickel Compounds** is finalized.

In addition, I am attaching to this letter a brief discussion—in question and answer format—of several issues that seemed to be of most interest or concern to BSC Subcommittee members when they considered the recommended listing of **Soluble Nickel Compounds** as a *known human carcinogen* in December 1998. I believe this attachment also helps demonstrate the need for further consideration of the listing recommendation for **Soluble Nickel**.

Sincerely,

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Director of Research

cc. Dr. C. Portier
Dr. K. Olden

Issues and Concerns Regarding the
Carcinogen Classification of Soluble Nickel

1. "Are the negative NTP inhalation studies with nickel sulfate hexahydrate in rats and mice relevant to humans?"

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 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 was raised at the December 1998 BSC Subcommittee meeting. First, it was 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. On these two bases, the negative studies by relevant route of exposure in two different species were dismissed. These concerns are addressed below.

With regard 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) in the two year bioassay 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 was sent to Dr. William Jameson of NTP on July 21, 2000. 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 this year. 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).

With regard to the second point, at the NTP BSC Subcommittee meeting in December 1998, it was pointed out 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. Furthermore, it was suggested that the differences in exposure levels could explain why rats did not get tumors in the NTP study while some workers did in the epidemiological studies.

To consider this point, it is crucial 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. 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 are 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). Using a slightly different approach, (RDDR, U. S. EPA 1994) similar conclusions were reached in the *TERA* 1999 Report (pages 45 and 66) and in Haber et al. (2000a, page 220).

2. "What is the significance of the intraperitoneal transplacental studies with nickel acetate for evaluating the carcinogenicity of soluble nickel compounds by relevant route of exposure (oral and inhalation)?"

There are a large number of negative animal carcinogenicity studies with water soluble nickel salts. In the recently conducted NTP inhalation study (NTP, 1996b), rats were exposed to $NiSO_4 \cdot 6H_2O$ at concentrations up to 0.11 mg Ni/m^3; mice were exposed to up to 0.22 mg Ni/m^3. These concentrations were chosen based on the toxicity observed in the 13-week studies and corresponded to the maximum tolerated doses (MTD). After two years of continuous exposure, there was no evidence of lung or nasal carcinogenic activity in mice or rats. Various combinations of non-carcinogenic lung effects were seen in both sexes in rats and mice. Five oral studies in mice, rats, and dogs (Schroeder *et al.*, 1964; Schroeder *et al.*, 1974; Schroeder and Mitchner, 1975; Ambrose *et al.*, 1976; Kurokawa *et al.*, 1985) have also been negative.

Less relevant routes of exposure such as intramuscular injection also gave negative results in rats (Gilman, 1962; Payne, 1964; Kasprzak *et al.*, 1983; Kasprzak, 1994). In an intraperitoneal injection study in rats, a relatively weak positive response at the injection site was reported by Pott and collaborators (1992). This finding was not reproduced in another intraperitoneal injection study conducted by Kasprzak *et al.* (1990). In this study, the administration of a soluble nickel compound by itself did not induce any kind of tumor, while the administration of the non-genotoxic carcinogen sodium barbital resulted in kidney tumors in male rats. When the soluble nickel compound was administered prior to sodium barbital, a higher number of kidney tumors (male rats) were induced (Kasprzak *et al.*, 1990). This phenomenon was later explained by the enhanced susceptibility of male rat kidneys to the sodium barbital effects, possibly involving the α-2 microglobulin mechanism (Kurata *et al.,* 1994). EPA and other regulatory agencies agree that this type of tumors should not be considered in carcinogenicity hazard assessment for humans. The results from Kasprzak *et al.* (1990) are consistent with a possible

"enhancing" role for soluble nickel in the kidney rather than an initiator/complete carcinogen role. These results are also in agreement with the results from the Kurokawa *et al.* (1985) study, in which oral administration of nickel chloride did not induce any kind of tumors, but it enhanced the formation of kidney tumors by N-ethyl-N-hydroxyethylnitrosamine (EHEN) in male rats.

Out of approximately a dozen animal studies, there is only one study, by one route of exposure, in one animal species that causes concern. This study is a transplacental rat carcinogenicity study in which rat dams were injected intraperitoneally with nickel acetate and the surviving pups were examined for tumors (Diwan *et al.*, 1992). In this study, intraperitoneal injection of nickel acetate by itself again failed to induce kidney tumors in the offspring of treated female rats. These results confirm the lack of kidney carcinogenicity seen with nickel acetate alone by Kazprzak *et al.* (1990). Surprisingly, the Diwan *et al.* study shows three-times as many pituitary tumors in offspring of nickel acetate treated rats (42%) than in offspring of those exposed to sodium acetate (13%). It should be noted that the historical data for the Fischer 344 rat indicate an average of 23 percent and 45 percent pituitary adenoma incidence for males and females, respectively (Haseman *et al.*, 1990). The observed increases in pituitary tumors in offspring of animals treated with nickel acetate may be explained by a disruption of the endocrine system due to the toxic effects of the Ni^{2+} ion (quite evident in this study with 88% pup mortality) rather than to a carcinogenic effect. It has been shown that in the rat, pituitary tumors can occur as a consequence of hormonal disruption (Mennel, 1978).

The lack of pituitary tumors in other studies (with soluble and insoluble nickel compounds) such as the transplacental study by Sunderman *et al.* (1981), intraperitoneal study by Kasprzak *et al.* (1990), oral studies by Ambrose *et al.* (1976), Schoeder and Mitchener (1975), and the inhalation NTP studies (NTP 1996 a,b,c) is consistent with this explanation. In addition no evidence of increased incidence of pituitary tumors has been found in human epidemiologic studies (over 50,000 workers). In the context of a dozen negative studies, the relevance of intraperitoneal studies for the carcinogenic assessment of soluble nickel compounds should be seriously questioned. This is particularly true when well-conducted inhalation studies are negative.

3. "How can the genotoxicity of soluble nickel compounds found in *in vitro* studies be reconciled with the general lack of carcinogencity of soluble nickel compounds in 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 see 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. Current models for nickel-mediated induction of respiratory tumors suggest that the main determinant of the respiratory carcinogenicity of a nickel compound is likely to be the bioavailability of the Ni (II) ion at nuclear sites of target epithelial cells (Costa, 1991; Oller *et al.*, 1997; *TERA* 1999; 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 be expected to experience severe respiratory toxicity before high enough levels are achieved at target nuclear sites. The available animal data support this contention.

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.

4. "How do the human epidemiological data fit together with the negative animal data and mechanistic information?"

Historically, inhalation exposure to very high concentrations of certain nickel compounds in the nickel producing industry has been associated with an excess of respiratory cancer. Epidemiological studies reveal that **only respiratory tumors** have been consistently associated with inhalation exposure to certain nickel compounds. Based on data from ten different cohorts the report of the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990) concluded that more than one form of nickel can give rise to lung and nasal cancer and that much of the respiratory cancer risk seen among nickel refinery workers could be attributed to

exposure to a mixture of oxidic and sulfidic nickel, at very high concentrations (≥ 10 mg Ni/m^3). The ICNCM also concluded that the carcinogenicity of soluble nickel acting alone could not be ruled out, but the evidence to support this hypothesis was unclear and somewhat contradictory. The ICNCM report suggested that an explanation for the contradictions was that soluble nickel exposure increases the risk of respiratory cancer by enhancing risks associated with exposures to less soluble forms of nickel.

An association between soluble nickel exposures and increased respiratory cancer risk was seen again in more recent updates of some of these cohorts (Andersen *et al.*, 1996, Anttila *et al.,* 1998). However, since mixed exposures to more insoluble nickel compounds and/or cigarette smoking are present in these cohorts, it is not possible to use these data to determine whether soluble nickel exposures alone can cause cancer or if they merely act to enhance the risks of known carcinogens. All of the 32 cases of nasal cancer reported in Andersen *et al.* (1996) were employed before 1956. It was only after this year that nickel oxide concentrations declined from 10 to 5 mg Ni/m^3/year. Only twenty of the 32 nasal cancer cases also had exposures to soluble nickel. Lung cancer was more strongly associated with exposure to soluble nickel in the presence of oxidic nickel than with exposure to soluble nickel alone. The overall data are consistent with i) exposures to both oxidic and soluble nickel compounds and ii) smoking and exposure to soluble nickel compounds resulting in higher lung cancer risk, but the data are insufficient to determine the effect of soluble nickel alone. The Anttila *et al.* (1998) also reports increased SIR for respiratory cancer in nickel refinery workers exposed to soluble nickel compounds. However, these cases cannot be attributed solely to soluble nickel exposures for several reasons. First, the nasal cancer cases had concomitant exposure to sulfidic nickel, wood dust or strong acid mists. Second, the lung cancer cases were employed prior to 1975; up to that time, sources of insoluble nickel were in close proximity to the electrolysis process. Moreover, some of the cases had worked both in the smelter and refinery. Third, the effect of smoking on lung cancer was not accounted for. The only epidemiologic studies of workers exposed almost exclusively to soluble nickel are those of nickel platers (Sorahan *et al.,* 1987; Pang *et al.,* 1996). These studies are small (in terms of workers), but they provide no evidence to suggest that soluble nickel exposure increases respiratory cancer risk.

The NTP inhalation studies of rats and mice indicate that exposure to soluble nickel compounds can induce respiratory toxicity manifested by inflammation and fibrosis in rats and mice. Chronic inhalation of soluble nickel at concentrations above those that cause chronic inflammation does not appear to produce tumors but it may enhance the carcinogenicity of concomitant exposures to respiratory carcinogens such as nickel subsulfide, certain nickel oxides and/or cigarette smoke. Exposures to concentrations of soluble nickel compounds below the threshold for respiratory toxicity would not be expected to enhance carcinogenic effects of other substances. **Together, the negative animal data, in conjunction with the epidemiological and mechanistic data suggest a possible enhancing rather than a direct carcinogenic role for soluble nickel compounds.**

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