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Neil J. King

+1 202 663 6061 (t)

+1 202 663 6363 (f)

neil.king@wilmerhale.com

May 15, 2008



TSCA Confidential Business Information Center (7407M)  
EPA East - Room 6428 Attn: Section 8(e)  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460-0001



Dear Sir/Madam:

Pursuant to Section 8(e) of the Toxic Substances Control Act, 15 U.S.C. § 2607(e), the Nickel Producers Environmental Research Association ("NiPERA"), on behalf of itself and its members in the Nickel Institute, hereby submits the April 29, 2008 audited final report of a carcinogenicity study of nickel metal powder administered by whole-body inhalation to Wistar rats. The study – which was sponsored by NiPERA, Eurofer, the International Stainless Steel Federation, WV Stahl, and WV Metalle – was conducted at WIL Laboratories in Ashland, Ohio, in accordance with recommended guidelines for such studies, including OECD Test Guideline 451. The pathology findings for the study were peer reviewed by an independent pathologist (R. Keenan, Charles River Laboratories-Pathology Associates), and the overall report for the study was reviewed by an Expert Group consisting of: Dr. G. Oberdörster (Rochester University, USA), Dr. U. Heinrich (Fraunhofer Institute, Germany), Dr. A. Gamer (BASF, Germany), Dr. V Schultz-Kemp (Thyssenkrupp Nirosta, Germany), Dr. D. Broeckman (WvMetalle, Germany), Dr. P. Koundakjian (Eurofer, ISSF, Belgium), Dr. A. Oller

Wilmer Cutler Pickering Hale and Dorr LLP, 1875 Pennsylvania Avenue NW, Washington, DC 20006  
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(NiPERA, USA), Dr. H. Bates (NiPERA, USA), and Dr. D. Kirkpatrick (WIL Laboratories, USA).

### **The Study**

The full study report is contained in electronic form on the enclosed compact disc. The main conclusions of the study, as summarized in Chapter 1, are as follows (emphasis added):

“Systemic effects of metallic nickel powder (elemental nickel) administered via 6-hour whole-body inhalation exposures, 5 days/week, for up to 24 consecutive months to Wistar rats were observed at exposure levels of 0.1, 0.4 and 1.0 mg/m<sup>3</sup> as evidenced by excessive mortality (0.4 and 1.0 mg/m<sup>3</sup>), clinical signs, body weight deficits, lower food consumption (0.4 and 1.0 mg/m<sup>3</sup>), higher WBC, neutrophil and RBC counts and higher hemoglobin and hematocrit values, higher adrenal gland weights (0.4 mg/m<sup>3</sup>) and microscopic findings in the adrenal glands, spleen, bone marrow, kidneys and bronchial and mediastinal lymph nodes. The systemic effects were most likely secondary to direct pulmonary toxicity. For example, clinical signs of increased respiration and blue extremities, body and/or facial area, higher RBC count, hemoglobin level and hematocrit, extramedullary hematopoiesis in the spleen and hypercellularity of the bone marrow were considered to be [sic] secondary to tissue hypoxia resulting from proteinosis and inflammation in the lungs. Local effects in the respiratory tract were limited to the lungs and included alveolar proteinosis, alveolar histiocytosis, chronic or chronic active inflammation, bronchiolo-alveolar hyperplasia and squamous cysts.

The number of animals surviving at 24 months in the control group and in the 0.1 and 0.4 mg/m<sup>3</sup> groups was sufficiently high for both males and females to meet the OECD guideline criterion and to permit a valid carcinogenicity assessment. **Chronic inhalation of metallic nickel for 83 to 104 weeks (approximately 19-24 months) was not carcinogenic to the lungs or any other respiratory tract tissue of Wistar rats after a study-duration of 30 months.**

Pheochromocytomas of the adrenal medulla in males were nickel exposure-related. However, the increased incidence of pheochromocytomas was likely secondary to increased catecholamine release due to hypoxia resulting from proteinosis and inflammation in the lungs. Increases in this adrenal medullary neoplasm have been reported in carcinogenicity studies with several chemicals that produce chronic lung injury (Ozaki, et al., 2002)."

Consistent with the conclusion that pheochromocytomas in the present study were secondary to chronic lung injury and hypoxia, no increases in adrenal medullary tumors were observed in an oral carcinogenicity study of nickel sulfate that resulted in much higher blood nickel levels than those found in the present study but had no lung toxicity (Heim *et al.*, 2007).

### **Weight of Evidence for Carcinogenicity of Nickel Metal**

The negative findings from the present animal carcinogenicity study of nickel metal powder by inhalation are consistent with the results of epidemiological studies involving workers exposed to metallic nickel (either alone or in conjunction with other nickel species). A comprehensive review and analysis of the pre-1990 literature on

nickel-exposed workers conducted by the International Committee on Nickel Carcinogenesis in Man ("ICNCM") did not find an association between exposure to nickel metal powder via inhalation and excess respiratory cancer risk (ICNCM 1990). A recent review of post-1990 epidemiological studies, which included much larger cohorts of refinery and non-refinery workers (Sivulka, 2005), confirms the ICNCM's conclusions, finding no association between exposure to nickel metal powder via inhalation and excess respiratory cancer risk. The most significant cohorts for purposes of evaluating exposures to metallic nickel are workers involved in stainless steel and alloy production (due to the large number of workers employed) and workers in the production of barrier material for use in uranium enrichment (whose nickel exposures consisted solely of relatively high levels of a high purity metallic nickel powder). None of these studies provide evidence that metallic nickel is a human carcinogen. Based on a review of these studies and the ICNCM's findings, Sivulka (2005) reaches the conclusion that metallic nickel exposure does not appear to increase the risk of respiratory cancer among exposed workers. The negative results of the current animal bioassay support that conclusion. It also should be noted that, with the exception of nickel powders (used largely as intermediates in manufacturing), nickel metal products produced from primary nickel refining are in massive form and cannot be inhaled.

Together, the combined animal and human data strongly indicate that nickel metal powder is not a human carcinogen via inhalation. Moreover, because the absorption of nickel ions from oral exposure to nickel metal has been shown to be lower

than the absorption of nickel ions from oral exposure to soluble nickel sulfate hexahydrate (Ishimatsu *et al.*, 1995; Hayman *et al.*, 1984), the negative oral carcinogenicity results for the latter compound (Heim *et al.*, 2007) would apply to nickel metal as well. This would indicate that nickel metal is not expected to be a human carcinogen by any relevant route of exposure.<sup>1/</sup>

### Toxicity Findings

Chronic inhalation exposure to nickel metal powder (MMAD = 1.8  $\mu\text{m}$ , GSD = 2.4  $\mu\text{m}$ ) at levels of 0.1 mg Ni/m<sup>3</sup> and above resulted in non-malignant lung alterations such as alveolar proteinosis, alveolar histiocytosis, and chronic inflammation. The toxicity seen in the lungs of rats in the present study is not unexpected based on earlier results from inhalation studies with nickel metal powder conducted in rabbits (Johansson *et al.*, 1981; 1983) and rat inhalation studies with nickel subsulfide, nickel oxide, and nickel sulfate hexahydrate (NTP 1996a,b,c).

If you have any questions about this submission, please let me know.

Very truly yours,



Neil J. King  
Counsel for the Nickel Producers  
Environmental Research Association

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<sup>1/</sup> In 1999, IARC concluded that there was "sufficient evidence in experimental animals for the carcinogenicity of implants of metallic nickel and for nickel alloy powder containing approximately 66-67% nickel, 13-16% chromium and 7% iron." This is an iatrogenic exposure. Powder or pure nickel metal implants are not a relevant route of exposure to nickel metal since pure nickel metal in powder or massive forms do not have any medical application.

References:

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TSCA Confidential Business Information Center (7407M)

May 15, 2008

Page 7 of 7

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