The Nickel Ion Bioavailability Model of the Carcinogenic Potential of Nickel-Containing Substances

Prepared for

Nickel Producers Environmental Research Association
2605 Meridian Parkway, Suite 120
Durham, NC 27713

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Abstract

The inhalation of nickel dust has been associated with an increased risk of respiratory cancer in workplaces that process and refine sulfidic nickel mattes, where workers are exposed to mixtures of sulfidic, oxidic, water-soluble, and metallic forms of nickel. Because there is great complexity in the physical and chemical properties of nickel species, it is of interest which specific nickel forms are associated with carcinogenic risk. Animal inhalation bioassays have been conducted on four nickel-containing substances and, based on the results from these studies, a bioavailability model for tumor induction by nickel is proposed. Contrary to the nickel ion theory, which holds that exposure to any nickel-containing substance leads to an increased cancer risk that is proportional to that substance's solubility, the nickel ion bioavailability model holds that a nickel-containing substance must release nickel ions that then become bioavailable at the nucleus of epithelial respiratory cells for the substance to be carcinogenic, and that the carcinogenic potency of the substance is proportional to the degree to which the nickel ions are bioavailable at that site. The bioavailability of nickel-containing substances depends on their respiratory toxicity, clearance, intracellular uptake, and both extracellular and intracellular dissolution. Although some data gaps were identified, a weight-of-evidence evaluation indicates that the nickel ion bioavailability model may explain the existing animal and *in vitro* data better than the nickel ion theory. Epidemiological data are not sufficiently robust for determining which model is most appropriate, but are consistent with the nickel ion bioavailability model. Information on bioavailability should be incorporated into future risk assessments.