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Systematic Review of the Potential Respiratory Carcinogenicity of Metallic Nickel in Humans

The inhalation of dust containing certain nickel compounds has been associated with an increased risk of lung and nasal cancers in occupational studies of workers who process or refine sulfidic nickel ores and are exposed to relatively high levels of mixtures of water-soluble, sulfidic, oxidic, and/or metallic forms of nickel. Nickel compounds are classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC), while metallic nickel is classified as a Group 2B carcinogen. IARC has identified metallic nickel as a priority substance for review within the next 5 years. We conducted a systematic review of the potential carcinogenicity of metallic nickel, focusing on cancers of the respiratory tract, which is the target organ for tumors induced by nickel compounds. We evaluated the quality and risk of bias of the relevant epidemiology, experimental animal, and *in vitro* mechanistic studies using the National Toxicology Program's Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool. We then used a systematic review protocol based on the OHAT approach to critically assess whether metallic nickel should be considered a human respiratory carcinogen. Our evaluation of the epidemiology evidence indicates that there is no increased risk of respiratory cancers in workers exposed predominantly to metallic nickel. In addition, cross-classification analyses of worker cohorts exposed to multiple forms of nickel indicate that there is no evidence to suggest that metallic nickel exposure resulted in increased respiratory cancer risk. Animal evidence indicates that metallic nickel does not increase the incidence of respiratory tumors in rodents exposed by inhalation. The mechanistic evidence indicates that metallic nickel can induce DNA strand breaks *in vitro*, but is not mutagenic, suggesting that any DNA damage induced by metallic nickel is repaired. Nevertheless, *in vitro* studies are limited in value, as they bypass normal clearance mechanisms and do not consider the low bioavailability of nickel ions from metallic nickel particles in the cell nucleus. After integrating the evidence from all study types, and applying a standard framework for causality, we concluded that any relationship between metallic nickel exposure and respiratory cancer in humans is not likely to be causal.