935 Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for Nickel

http://www.atsdr.cdc.gov/ToxProfiles/tp15.pdf

In vitro toxicology – p. 132-133, 154, 156, 176

Dermal/inhalation carcinogenicity – p. 13, 27, 57, 79-89, 130, 138, 174-176

Cardiovascular toxicity – p. 69, 109, 123

Inhalation studies – p. 17-22, 27-89, 134-135, 138-140, 142-143, 160, 205, 211, 244, 279

Reprotoxicity & development toxicity – p. 13, 22-23, 77-79, 93, 98, 118-122, 125, 129-130, 176-177

Summary of Health Effects

The general population can be exposed to nickel via inhalation, oral, and dermal routes of exposure. Based on occupational exposure studies, reports of allergic contact dermatitis, and animal exposure studies, the primary targets of toxicity appear to be the respiratory tract following inhalation exposure, the immune system following inhalation, oral, or dermal exposure, and possibly the reproductive system and the developing organism following oral exposure.

The most commonly reported adverse health effect associated with nickel exposure is contact dermatitis. Contact dermatitis is the result of an allergic reaction to nickel that has been reported in the general population a nd workers exposed via dermal contact with airborne nickel, liquid nickel solution, or prolonged contact with metal items such as jewelry and prosthetic devices that contain nickel. After an individual becomes sensitized to nickel, dermal contact with a sm all amount of nickel or oral exposure to fairly low doses of nickel can result in dermatitis. Approximately 10 –20% of the general population is sensitized to nickel.

Adverse respiratory effects have been reported in humans and animals exposed to nickel co mpounds at concentrations much higher than typically found in the environment. The available data on noncancerous respiratory effects in humans are limited. In nickel workers, exposure to nickel did not result in increases in the risk of death from nonmali gnant respiratory system disease. Studies examining potential nonlethal respiratory effects have not found consistent results. Animal data provide strong evidence that nickel is a respiratory toxicant; lung inflammation is the predominant effect. Evidence of lung inflammation has been observed following acute-, intermediate-, and chronic-duration exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide. Nickel sulfate was the most toxic of the three compounds and nickel oxide was the least tox ic. For all three compounds, the threshold for lung

effects decreased as the duration of exposure increased. Exposure to nickel sulfate or nickel subsulfide also produced damage to the nasal olfactory epithelium. Human and animal data provide strong eviden ce that inhalation exposure to some nickel compounds can induce lung cancer. As described in greater detail later in this section, carcinogenic responses have been observed following inhalation exposure to nickel subsulfide and nickel oxide; in the absence of exposure to other carcinogenic agents, nickel sulfate does not appear to be carcinogenic following inhalation exposure.

The potential for nickel compounds to induce reproductive effects has not been firmly established. Several animal studies have repo rted adverse effects in the male reproductive system following oral exposure to nickel sulfate, nickel chloride, or nickel nitrate. The observed effects included histological alterations in the epididymis and seminal vesicles, decreases in sperm concentration, motility, and abnormalities, and decreases in fertility following male exposure, but not female only exposure. However, the poor reporting of study results, particularly incidence data and statistical analysis, limits the interpretation of these studi es. Additionally, other studies have not found histological alterations in the male reproductive system following long-term oral exposure or impaired fertility following oral exposure. A number of studies have reported decreases in survival of the offsprin g of animals exposed prior to mating and during the gestation and lactation periods. Interpretation o f these data are complicated by maternal toxicity, particularly decreases in body weight gain, which frequently occurred at the same dose levels.

The most consistently reported adverse effects resulting from exposure to nickel are contact dermatitis and respiratory effects, including cancer; a more detailed discussion of these effects follows. The reader is referred to Section 3.2, Discussion of Health Effe cts by Route of Exposure, for additional information on other health effects.

Contact Dermatits. Nickel sensitivity is a form of delayed hypersensitivity that is found in 10 –20% of the general population. The prevalence of nickel sensitivity is higher amo ng young women than any other segment of the population, which is probably the result of higher rates of ear and other types of body piercing rather than increased susceptibility to sensitization. There is some evidence of a genetic susceptibility factor t hat may predispose certain individuals to the development of nickel sensitivity. A significant increase in human leukocyte antigen (HLA)-DRw6 antigens were found among individuals with nickel contact dermatitis compared to individuals with no history of at opy or contact dermatitis. The relative risk of individuals with the HLA-DRw6 allele developing nickel sensitivity was estimated to be 3.3.

Nickel sensitization typically involves initial prolonged contact with nickel or exposure to a very large nickel do se. In the general population, the initial nickel contact often comes from body piercing with jewelry that releases large amount of nickel ions. The resulting dermatitis, which is an inflammatory reaction mediated by type IV hypersensitivity, typically occ urs beneath the metal object. With repeated exposure, the area of sensitization can spread to other locations, particularly the hands. Shorter contact with nickel items, such

as nickel-plated coins or door handles, does not result in nickel sensitization. After an individual becomes sensitized to nickel, much lower concentrations are needed to elicit a response. There is limited information on nickel levels resulting in sensitization. One study found that the sensitizing nickel level was 100–1,000 times higher than the level eliciting dermatitis in a previously sensitized individual. Among sensitized individuals, a direct relationship between nickel exposure level and severity of the dermatitis has been found. A weak reaction has been reported in individuals exposed to nickel alloys that release nickel ions at a rate of <0.5 µg/cm2/week; a strong reaction was observed for nickel alloys that release >1 µg/cm2/week. No reaction was seen in nickel-sensitized subjects undergoing patch testing with 0.01% nickel as nickel sulfate in petrolatum; however, exposure to 0.03% nickel resulted in dermatitis. Similarly, an oral challenge dose of 0.02 mg Ni/kg can induce dermatitis in a small percentage of nickel-sensitized individuals, whereas exposure to higher doses (0.06 mg Ni/kg) will often result in dermatitis in most nickel-sensitized individuals. Exposure to these nickel concentrations will not result in dermatitis in nonsensitized individuals.

Respiratory Effects. Both noncancerous and cancerous respiratory effects have been observed in humans and animals exposed to airborne nickel compounds. Chronic bronchitis, emphysema, pulmonary fibrosis, and impaired lung function have been observed in nickel welders and foundry workers. These effects were not consistently seen across studies, and co-exposure to other toxic metals such as uranium, iron, lead, and chromium confounds the interpretation of the results. Studies examining the risk of death from nonmalignant respiratory disease among nickel workers have not found significant increases; however, many studies found that the number of observed deaths were significantly lower than expected, suggesting a healthy worker effect.

In animals, the predominant noncancerous effect is lung inflammation following exposure to nickel sulfate, nickel subsulfide, and nickel oxide. The toxicity of nickel in the respiratory tract appears to be related to the solubility of the individual nickel compounds, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The pulmonary toxicity appears to be related to exposure concentration rather than nickel lung burden. It has been postulated that the higher toxicity of soluble nickel is due to the higher concentrations of free nickel ions, which can diffuse across the cell membrane and interact with cytoplasmic proteins. In contrast, insoluble nickel compounds are phagocytized and a smaller amount of nickel ions interact with cytoplasmic proteins. Following an intermediate-duration exposure, the respective no-observed-adverse effect level (NOAEL) and lowestobserved-adverse effect level (LOAEL) values for lung inflammation were 0.06 and 0.11 mg Ni/m3 for nickel sulfate, 0.11 and 0.22 mg Ni/m3 for nickel subsulfide, and 2 and 3.9 mg Ni/m3 for nickel oxide. At approximately 0.4 mg Ni/m3 as nickel sulfate, nickel subsulfide, and nickel oxide, the lung burdens following a 13-week exposure were 6, 7, and 80 µg Ni/g lung, respectively. For all durations and nickel compounds tested, rats appear to be more sensitive to the lung effects than mice; significant increases in the incidence of lung inflammation were observed at lower concentrations in the

rats than mice. However, mice were more susceptible to the lethal effects (presumably from impaired lung function) than ra ts. In addition to the pulmonary effects, atrophy of the nasal olfactory epithelium was observed in rats exposed to nickel sulfate or nickel subsulfide for acute, intermediate, and chronic durations; nasal effects were not observed following exposure to nickel oxide.

The carcinogenicity of nickel has been well documented in occupationally-exposed individuals. Significant increases in the risk of mortality from lung or nasal cancers w ere observed in several cohorts of nickel refinery workers. Studies of wor kers in other nickel industries, including nickel mining and smelting, nickel alloy production, stainless steel production, or stainless steel welding, which typically involve exposure to lower concentrations of nickel, have not found significant increases in cancer risks. In most of the occupational exposure studies, the workers were exposed to several nickel species, thus making it difficult to compare carcinogenic potential across nickel species. An extensive re-evaluation of the studies published prior to 1990 found the strongest evidence of carcinogenicity for sulfidic nickel; exposure to high concentrations (>10 mg Ni/m3) resulted in increased lung cancer risks. There is weaker evidence that high concentrations (>10 mg Ni/m3) of oxidic nickel, particul arly when there is co-exposure to soluble nickel, is also carcinogenic. Soluble nickel does not appear to be carcinogenic in the absence of exposure to other carcinogenic agents. There is no evidence that exposure to low levels of nickel is carcinogenic in humans. The conclusions drawn from the occupational exposure studies are supported by animal inhalation studies. Significant increases in the incidence of lung tumors were observed in rats chronically exposed to nickel subsulfide or nickel oxide. The carc inogenic response was stronger for nickel subsulfide compared to nickel oxide. In contrast, no increases in lung tumor incidences were observed in rats exposed to nickel sulfate; however, the highest concentration tested (0.11 mg Ni/m3) was lower than the cancer effect levels for nickel subsulfide (0.73 mg Ni/m3) or nickel oxide (1 mg Ni/m3).

Although the evidence is sufficient to consider less-soluble nickel compounds as carcinogens following inhalation exposure, how environmental exposure to nickel affec ts cancer risk is not clear. Nickel levels in the environment are much lower than those that were associated with cancer in workers. In the environment, nickel is also more likely to be in the form of a mineral lattice rather than the more active nickel re finery dust that contains nickel subsulfide, the form of nickel most consistently associated with cancer. Although soluble nickel compounds may not be directly carcinogenic, as indicated by the negative results in the nickel sulfate bioassay, inhalation of nickel sulfate did result in an inflammatory response in the lungs of animals. Because sustained tissue damage can serve to promote carcinogenesis, epidemiology studies of humans who are exposed to many substances may not be able to distinguish between the carcinogenic activity of less-soluble nickel compounds and the promoting activity of toxic concentrations of soluble nickel compounds.

The Department of Health and Human Services has determined that metallic nickel may reasonably be anticipated to be a h uman carcinogen and nickel

compounds are known to be human carcinogens. Similarly, IARC classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery du st and nickel subsulfide in Group A (human carcinogen). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk l evels of 2.4x10-4 (µg/m3)-1 and 4.8x10-4 (µg/m3)-1 were derived by EPA for nickel refinery dust and nickel subsulfide, respectively.