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Project Summary

Health Assessment Document for Nickel

The predominate atmospheric forms of nickel are as sulfate, oxides, and complex oxides. Nickel also occurs in ambient and drinking water and soils.

Routes of intake for man are inhalation, ingestion, and percutaneous absorption. Pulmonary absorption varies according to chemical and physical form of the compound. While gastrointestinal intake ranges from 300 to 500 µg daily, absorption is only one to ten percent of intake. Percutaneous absorption, usually through contact with nickel alloys in the household, is related to hypersensitivity and skin disorders. Inhaled nickel compounds lead to highest levels in lung, brain, kidney and liver.

Nickel exposure produces chronic dermatological, respiratory, endocrine and cardiovascular effects. Reproductive and developmental effects have been found in animals but not humans. Various nickel compounds have been tested for mutagenicity, demonstrating the ability of nickel compounds to produce genotoxic effects; the translation of these effects into actual mutations is still not clearly understood. There is evidence both in humans and animals for the carcinogenicity of nickel in some forms. Lifetime cancer risks for continuous inhalation exposure at 1 µg nickel/m^3 have been estimated for nickel refinery dust and nickel subsulfide.

There is a growing evidence that nickel may be an essential element for humans.

This Project Summary was developed by EPA's Environmental Criteria and Assessment Office, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Background

Chemical/Physical Properties of Nickel and Nickel Compounds

Nickel is found in nature as a component of silicate, sulfide, or, occasionally, arsenide ores. It is a valuable mineral commodity because of its resistance to corrosion and its siderophilic nature which facilitates the formation of nickel-iron alloys. Stainless steel is the most well-known alloy; others include permanent magnet and super alloys, used in radios, generators and turbochargers, and copper-nickel alloys, used when resistance to extreme stress and temperature is required. Other uses for nickel and its compounds include electroplating baths, batteries, textile dyes and mordants, and catalysts.

As a member of the transition metal series, nickel is uniquely resistant to alkalis, but generally dissolves in dilute oxidizing acids. Nickel may exist in many oxidation states, the most prevalent being Ni^{2+}. Of some commercial and/or environmental significance are several binary nickel compounds including nickel oxide (both black, which is chemically reactive, and green, which is inert and refractory) and complex oxides of nickel, nickel sulfate, nickel nitrate, nickel carbonate, nickel hydroxide, nickel sulfide, and nickel carbonyl.

Nickel in Ambient Air

In the atmosphere, nickel is present as a constituent of suspended particulate matter. The primary stationary source categories that emit nickel into ambient air are: primary production sources

(nickel ore mining/smelting and nickel matte refining); combustion and incineration sources (coal and oil burning units in utility, industrial, commercial and residential use sectors, and municipal and sewage sludge incinerators); high temperature metallurgical sources (steel manufacturing, nickel alloy manufacturing, secondary nickel smelting, secondary nonferrous metals smelting, and iron and steel foundries); chemical and catalyst sources (nickel chemical manufacturing, electroplating, nickel-cadmium battery manufacturing and catalyst production, use and reclamation); and miscellaneous sources (co-product nickel recovery, cement manufacturing, coke ovens, asbestos mining/milling and cooling towers).

While nickel in its elemental state can be measured in the ambient air, determination of specific compounds is difficult to achieve. Techniques used to break down inorganic compounds into their ionic or atomic states change the form of the compound in the attempt to determine the total concentration of the element. In addition, the very low level of nickel present in ambient air samples (average of 0.008 μg/m^3; 1982 figures) complicates the situation. Nevertheless, by analyzing the physical and chemical properties of nickel, the forms of nickel input to various source processes, and the reaction conditions encountered in various source categories, it is possible to estimate forms of nickel emitted into the ambient air. From such analyses, the predominant forms appear to be nickel sulfate, complex oxides of nickel and other metals (chiefly iron), nickel oxide, and to a much lesser extent, metallic nickel and nickel subsulfide. Of the total volume of nickel emitted into the ambient air, the greatest contribution is from the combustion of fossil fuels in which nickel appears to be in the form of nickel sulfate, followed by lesser amounts of nickel oxide and complex metal oxides containing nickel.

Nickel in Ambient and Drinking Water

Nickel is usually found as Ni^{2+} in aquatic systems. Chemical factors which can affect the form of nickel in aquatic systems include pH and the presence of organic and inorganic ligands. Nickel is found in ambient waters as a result of chemical and physical degradation of rocks and soils, deposition of atmospheric nickel-containing particulate matter, and direct (and indirect) discharges from industrial processes. Of the anthropogenic sources of nickel in water, primary nickel production, metallurgical processes, fossil fuel combustion and incineration, and chemical and catalyst production are predominant.

Measurements of nickel in aqueous environments are generally reported as total nickel. The mean concentration of nickel in U.S. surface waters (based upon 1982 figures) ranges from less than 5 μg/l in the Great Basin of southern Nevada to greater than 600 μg/l in the Ohio River Basin. Concentrations in groundwater are also highly variable with means ranging from 4430 μg/l in the Ohio River basin to 2.95 μg/l in the Upper Mississippi River basin (based upon 1982 figures). A mean nickel concentration of 4.8 μg/l has been calculated for drinking water from eight metropolitan areas (based upon 1970 figures).

Specific forms of nickel in ambient waters have not been reported; however, inferences of species expected to be found in effluents can be made based on the nature of source processes and the aqueous chemistry of nickel. Nickel species in wastewaters from the major anthropogenic sources are likely to include dissolved salts (such as sulfates, chlorides and phosphates), insoluble oxides of nickel and other metals, and metallic nickel powder.

Nickel in Soil and Sediment

Many of the same chemical and physical properties which govern the behavior of nickel in aqueous environments also affect the behavior of nickel in soils and sediments. In soils, nickel may exist in several forms such as inorganic crystalline minerals or precipitates, as free ion or chelated metal complexes in soil solution, and as complexed with, or adsorbed to, inorganic cation exchange surfaces such as clays.

Naturally occurring nickel in soils depends upon the elemental composition of rocks in the upper crust of the earth. The natural concentration of nickel in soils usually ranges from 5 to 500 ppm, with an average level estimated at 50 ppm. Soils derived from serpentine rock (naturally high in nickel content) may contain nickel levels up to 5000 ppm. Anthropogenic sources of nickel to soils include emissions from primary smelters and metal refineries, disposal of sewage sludge or application of sludge as a fertilizer, auto emissions, and emissions from electric power utilities; the most significant of these sources being smelting and refining operations and sludge applications. Depending upon t source, nickel soil concentrations ha been reported to range from 0.90 pp (from auto emissions) to as much 24,000 ppm (near metal refineries) 53,000 ppm (from dried sludge). The figures are based upon elemental nic as specific forms of nickel in soils ha not been reported.

Nickel in Plants and Food

The primary route for nic accumulation in plants is through r uptake from soil. Nickel is present vegetation usually below the 1 ppm le although plants grown in serpentine s have been shown to have nic concentrations as high as 100 ppm. crops grown in soils where sew sludge has been applied, nic concentrations have been reported range from 0.3 to 1150 ppm.

In addition to nickel uptake via s food processing methods have b shown to add to nickel levels alre present in foodstuffs via leaching f nickel-containing alloys in fo processing equipment, the milling flour, and the catalytic hydrogenatio fats and oils by use of nickel catal The nickel content of various classe food has been reported to range 0.02 ppm (wet weight) in food items as fresh tomatoes, frozen swordfish pork chops to 9.80 ppm in cocoa.

The Global Cycling of Nickel

Nickel in all environme compartments is continuously transf between compartments by na chemical and physical processes su weathering, erosion, runoff, precipit stream/river flow and leaching. N introduced into the environmen anthropogenic means is subject t same chemical and physical proce but can account for increased an concentrations in all environm compartments. The ultimate sin nickel is the ocean; however, the cy continuous because some nicke leave the ocean as sea spray ae which burst and release minute containing particles into the atmosp

Nickel Metabolism

Absorption

Routes of nickel intake for ma animals are inhalation, ingestio percutaneous absorption. Pare exposure of experimental anim mainly of importance in assessir kinetics of nickel transport, distri and excretion. Parenteral expos

humans to nickel from medications, emodialysis and protheses can be a significant problem to certain sections of the population.

The relative amount of inhaled nickel which is absorbed from various compartments of the pulmonary tract is a function of both chemical and physical forms. Insoluble particulate nickel deposited in the various respiratory compartments in both occupationally exposed subjects and the general population is very slowly absorbed with accumulation over time. Experimental animal data show very slow clearance of deposited insoluble nickel oxide from the respiratory tract, moderate clearance (around 3 days) of the carbonate and rapid clearance (hours to several days) of soluble nickel salts. In the case of nickel oxide, clearance from lung involves both direct absorption into the blood stream and clearance via the lymphatic system. While most respiratory absorption studies demonstrate that differences in compound solubilities relate to pulmonary clearance, with inert compounds having relatively slower clearance, the relationship of respiratory absorption to pathogenic effects is still not clearly understood.

Gastrointestinal intake of nickel by man is relatively high compared to other toxic elements and can be partially accounted for by contributions of nickel from utensils and equipment in processing and home preparation of food. Average human dietary values range from 300 to 500 µg daily with absorption in the order of one to ten percent. Recent studies show that nickel bioavailability in human diets appears to be dependent on dietary composition.

Percutaneous absorption of nickel occurs and is related to nickel-induced hypersensitivity and skin disorders; however, the extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time. Transplacental transfer of nickel has been evidenced in rats and mice and several reports indicate that such passage can also occur in man.

Transport and Distribution

The kinetic processes governing the transport and distribution of nickel in various organisms are dependent upon the modes of absorption, the rate and level of nickel exposure, the chemical form of nickel and the physiological status of the organism. Absorbed nickel is carried by the blood, and although the extent of partitioning between erythrocytes and plasma or serum cannot be precisely stated, serum levels can be useful indicators of blood burden and, to a more limited extent, exposure status (excluding exposure to insoluble and unabsorbed nickel deposited in lungs). In unexposed individuals, serum nickel values are approximately 0.2 to 0.3 µg/dl. Albumin is the main macromolecular carrier of nickel in a number of species, including man, while in man and rabbit there also appear to be nickel-specific proteins

Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in lung, brain, kidney, liver, and adrenals. Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver, and lung. Nickel absorption and tissue distribution following oral exposure appear to be dependent upon the relative amounts of the agent employed. Animal studies suggest that a homeostatic mechanism exists to regulate low levels of nickel intake (around 5 ppm), but that such regulation is overwhelmed in the face of large levels of nickel challenge

Based on animal studies, nickel appears to have a very short half-time in the body of several days with little evidence for tissue accumulation. Human studies have shown that age-dependent accumulation of nickel appears to occur only in the case of the lung with other soft and mineralizing tissues showing no accumulation. There are very few data concerning nickel tissue levels and total body burden in humans. One estimate is that the total nickel burden in man is about 10 mg.

Excretion

The excretory routes for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake. Unabsorbed dietary nickel is lost in the feces. Urinary excretion in man and animals is usually the major clearance route for absorbed nickel, with biliary excretion also occurring in experimental animals. Sweat can also constitute a major route of nickel excretion. Recent studies suggest that normal levels of nickel in urine vary from 2 to 4 µg/l

While hair deposition of nickel also appears to be an excretory mechanism, the relative magnitude of this route, compared to urinary excretion, is not fully known at present.

Factors Affecting Nickel Metabolism

A number of disease states or other physiological stresses can influence nickel metabolism in man. In particular, heart and renal disease, burn trauma, and heat exposure can either raise or lower serum nickel levels. To what extent factors such as age or nutritional status affect nickel metabolism in man is presently unknown. In animals, both antagonistic and synergistic relationships have been demonstrated for both nutritional factors and other toxicants.

Nickel Toxicology

Subcellular and Cellular Aspects of Nickel Toxicity

Nickel, as the divalent ion, is known to bind to a variety of biomolecular species, such as nucleic acids and proteins, as well as their constituent units. Strongest interactions occur with sulfhydral, aza- and amino groups with binding to peptide (amido) and carboxylate ligands also possible.

A number of reports in the literature describe various *in vivo* and *in vitro* effects of various nickel compounds on enzyme systems as well as nucleic acid and protein biosynthesis. In particular, effects are seen on drug- detoxifying enzymes in various tissues, enzymes that mediate carbohydrate metabolism and enzymes that mediate transmembrane transport, such as ATPase.

A number of ultrastructural alterations are seen in cellular organelles from experimental animals exposed to various nickel compounds Most of these changes involve the nucleus and mitochondria and range from slight changes in conformation to evidence of degeneration.

The behavior of cells in culture exposed to nickel compounds has been reported from different laboratories. Nickel ion, at varying levels, affects both viability and phagocytic activity of alveolar macrophages, which may explain the role of nickel in retarding resistance to respiratory tract infections in animal models.

Nickel-induced human lymphocyte transformation has been studied as a sensitive *in vitro* screening technique for nickel hypersensitivity and this procedure appears to be a reliable alternative to classical patch testing.

Various studies have been directed to the response of cells in culture to

insoluble nickel dusts which are implicated in human and experimental animal carcinogenesis. In particular, rat embryo myoblasts show drastic reduction of mitotic index and viability when exposed to nickel subsulfide.

Acute Effects of Nickel Exposure

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl, $Ni(CO)_4$, exposure to which has been through accidental release to nickel-processing workers. Acute nickel carbonyl poisoning is clinically manifested by both immediate and delayed symptomology. With the onset of the delayed, insidious symptomology there are constrictive chest pain, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Most of these symptoms strongly resemble those of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in both man and animals. The pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage, edema, and cellular derangement. Patients surviving an acute episode of exposure may be left with pulmonary fibroses.

Chronic Effects of Nickel Exposure

Dermatological Effects

Nickel dermatitis and other dermatological effects of nickel have been documented in both nickel worker populations and populations at large. Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological reports suggest that nonoccupational exposures to nickel-containing commodities may present significant problems to the general populace. Nonoccupational exposure to nickel includes nickel-containing jewelry, coins, tools, cooking utensils, stainless steel kitchens, prostheses, and clothing fasteners.

Clinically, nickel dermatitis is usually manifested as a papular or papulovesicular dermatitis with a tendency toward lichenification, having the characteristics of atopic rather than eczematous dermatitis. The hand eczema associated with nickel allergy appears to be of the pompholyx type, i..e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers.

A role for oral nickel in dermatitic responses by sensitive subjects has recently been described. Nickel-limited diets in one clinical trial resulted in marked improvement of hand eczema in half of the subjects while in a second study, nickel added to the diets of patients appeared to aggravate the allergic response. Further study of oral nickel-nickel sensitivity relationships should be conducted.

Nickel-containing implanted prostheses may provoke flare-ups of nickel dermatitis in nickel-sensitive individuals. The extent of this problem appears to depend on the relative ease with which nickel can be solubilized from the surface of the devices by action of extracellular fluid.

The underlying mechanisms of nickel sensitivity presumably include diffusion of nickel through the skin and subsequent binding of nickel ion.

Useful animal experimental models of nickel sensitivity are few and have been conducted only under very specialized conditions.

Respiratory Effects

Noncarcinogenic effects of nickel in the human respiratory tract mainly derive from studies of nickel workers in certain production or use categories who have been exposed to various forms of nickel. In the aggregate, assessment of available human and animal data show two areas of possible concern for humans: (1) direct respiratory effects such as asthma, nasal septal perforations, and chronic rhinitis and sinusitis; and (2) increased risk for chronic respiratory tract infections secondary to the effect of nickel on the respiratory immune system.

Endocrine Effects

A number of effects of nickel on endocrine-mediated physiological processes have been observed. In carbohydrate metabolism, nickel induces a rapid transitory hyperglycemia in rats, rabbits, and domestic fowl after parental exposure to nickel (II) salts. These changes may be associated with effects on alpha and beta cells in the pancreatic islets of Langerhans. Nickel also appears to affect the hypothalamic tract in animals, decreasing the release of prolactin. Decreased iodine uptake by the thyroid has also been observed when nickel chloride is inhaled or ingested. Human endocrine responses to nickel have been poorly studied, although hyperglycemia has been reported in workmen accidentally exposed to nick carbonyl.

Cardiovascular Effects

Experimental and clinical observ tions suggest that exogenous nickel ion, and possibly endogenous nickel has a marked vasoconstrictive action coronary vessels. Recent studies sh that such action may be operative patients with ischemic myocardial inj and in burn patients. Whether excessi nickel exposure in occupational nonoccupational populations co exacerbate ischemic heart disease enhance the risk of myocardial infarct in subjects with coronary artery dise is unknown but merits further study.

Reproductive and Developmen Effects

Exposure to nickel has been showr cause both reproductive a developmental effects in experime animals; however, such effects have been noted in man.

Specific reproductive effects seer male rats include degenerative chan in the testis, epididymis a spermatozoa. Limited studies in fen rats and hamsters suggest an effect embryo viability and the implanta process. Such effects have been note animals exposed to excess amount nickel. In contrast, it has b demonstrated that a deficiency of die nickel can also lead to reproduc effects in the form of reduced litter s and decreased viability of newborn.

With respect to developmental toxi nickel exposure of animals prio implantation has been associated delayed embryonic development possibly with increased resorpti Structural malformations have been n in avian species exposed to nickel s While similar malformations have been seen in mammals, the data been lacking in sufficient detail ma determinations about significa difficult. Teratogenic effects of n carbonyl in mammals have b demonstrated in two rodent species.

Mutagenic Effects

Various inorganic compounds of r have been tested for mutagenicity other genotoxic effects in a variety c systems. From these tests it appear nickel may induce gene mutatio bacteria and cultured mammalian however, the evidence is fairly we addition, nickel appears to in chromosomal aberrations in cul

mammalian cells and sister chromatid exchange in both cultured mammalian cells and human lymphocytes. However, the induction of chromosomal aberrations *in vivo* has not been observed. More definitive studies are needed to determine whether or not nickel is clastogenic. Nickel does appear to have the ability to induce morphological cell transformations *in vitro* and to interact with DNA resulting in crosslinks and strand breaks. In aggregate, studies have demonstrated the ability of nickel compounds to induce genotoxic effects; however, the translation of these effects into actual mutations is still not clearly understood.

Carcinogenic Effects

There is evidence both in humans and animals for the carcinogenicity of nickel, at least in some forms. The human evidence of a cancer risk is strongest via inhalation in the sulfide nickel matte refining industry. This evidence includes a consistency of findings across many different studies in several different countries, specificity of tumor site (lung and nose), high relative risks, particularly for nasal cancer, and a dose-response relationship by length of exposure. There are also animal and *in vitro* studies on nickel compounds which support the concern that nickel, at least in some forms, should be considered carcinogenic. The animal studies have employed mainly injection as the route of exposure with some studies using inhalation as the exposure route. While the majority of the compounds tested in the injection studies have caused tumors at the injection site only, nickel acetate, when tested in strain A mice, and nickel carbonyl, at toxic levels, have also caused distal site primary tumors. The relevance of injection site, only tumors in animals to human carcinogenic hazard via inhalation, ingestion, or cutaneous exposure is uncertain. Orally, in animals, three low-dose drinking water studies and one diet study with soluble nickel compounds have not shown any increase in tumors. Thus, nickel at least in some forms, should be considered carcinogenic to humans via inhalation, while the evidence via ingestion is inadequate.

Based on analysis of all the available data there are only three compounds or mixtures of nickel compounds that can currently be classified as either Group A (known human carcinogens) or B (probable human carcinogens), according to the Environmental Protection Agency's classification scheme for evaluating carcinogens . Nickel refinery dust from pyrometallurgical sulfide nickel matte refineries is classified as Group A. The fact that nickel subsulfide is a major nickel component of this refinery dust, along with the evidence from animal and *in vitro* studies, is sufficient to conclude that nickel subsulfide is also in Group A. While there is inadequate evidence from epidemiologic studies with regard to evaluating the carcinogenicity of nickel carbonyl, there is sufficient evidence from animal studies to classify it as Group B2. The carcinogenic potential of other nickel compounds remains an important area for further investigation. Some biochemical and *in vitro* toxicological studies seem to indicate the nickel ion as a potential carcinogenic form of nickel and nickel compounds. If this is true, all nickel compounds might be potentially carcinogenic with potency differences related to their ability to enter and make the carcinogenic form of nickel available to a susceptible cell. However, at the present time, neither the bioavailability nor the carcinogenesis mechanism of nickel compounds is well understood.

Quantitatively, several data sets from nickel refinery workers provide sufficient exposure-response information both for testing model fits and for estimating incremental unit cancer risk. While the data partially support the use of both the additive and multiplicative excess risk models, neither is entirely satisfactory. Using both models and four data sets, a range of incremental unit risks from 1.1 x 10^{-5} $(\mu g/m^3)^{-1}$ to 4.6 x 10^{-4} $(\mu g/m^3)^{-1}$ has been calculated. Taking the midpoint of this range, the quantitative incremental unit risk estimate for nickel refinery dust is 2.4 x 10^{-4} $(\mu g/m^3)^{-1}$; the quantitative unit risk estimate for nickel subsulfide, the most carcinogenic nickel compound in animals is twice that for nickel refinery dust. Comparing the potency of nickel subsulfide to 55 other compounds which the Environmental Protection Agency has evaluated as suspect or known human carcinogens, nickel subsulfide would rank between the second and third quartiles.

Other Toxic Effects

Except for acute fatal exposures to nickel carbonyl, nickel compounds appear to possess low general neurotoxic potential. Lesions observed in neural tissue by nickel carbonyl include diffuse punctate hemorrhages, neural fiber degeneration, and marked edema.

Nickel subsulfide, when administered intrarenally to rats, provokes a pronounced, dose-dependent erythrocytosis associated with erythroid hyperplasia in bone marrow.

The effects of nickel chloride on the cellular and humoral immune responses of mice have been studied. Of particular note is the ability of nickel chloride to suppress the activity of natural killer cells within 24 hours of a single intramuscular injection. Such cells are thought to be one of the first lines of nonspecific defense against certain types of infection and tumors.

Nickel as an Essential Element

There is a growing body of literature which establishes an essential role for nickel, at least in experimental animals.

One key criterion for element essentiality--existence of specific nickel-deficiency syndromes--is reasonably satisfied for nickel. Various researchers have shown different systemic lesions in various animals deprived of dietary nickel. Nickel deprivation has an effect on body weight, reproductive capability, and viability of offspring and induces an anemia through reduced absorption of iron. Both antagonistic and synergistic interactions of nickel with various compounds have been noted to affect nutritional requirements.

Nickel also appears to be required in several proteins and enzymes. Jack bean urease (and possibly rumen microbial urease) has been shown to be such an enzyme. Recent studies on the activation of the calmodulin-dependent phosphoprotein phosphatase, calcineurin, suggests that nickel II may play a physiological role in the structural stability and full activation of this particular enzyme.

Further information in support of nickel as an essential element is the apparent existence of a homeostatic mechanism for regulating nickel metabolism and the existence of nickel proteins in man and rabbit. Although the evidence for the role of nickel in human physiology is not conclusively established, the transitory rise in circulatory nickel observed shortly after parturition has been linked to a possible role in control of atonic bleeding and placental separation.

Populations at Risk

Among various subgroups of the U.S. population who may be at special risk for adverse effects of nickel are those who have nickel hypersensitivity and suffer chronic flare-ups of skin disorders with frank exposure. Within this category would be individuals predisposed to

sensitization to nickel by virtue of familial history. In terms of the extent of nickel exposure among hypersensitive individuals, women who are housewives seem to be at particular risk. However, no data base exists by which to determine the prevalence of nickel hypersensitivity in the general U.S. population.

The extent to which nickel in inhaled cigarette smoke is a cofactor in the demonstrated association of smoking with various respiratory disorders is not defined at present, since various studies have presented conflicting information.

Nickel crosses the placental barrier in animals and apparently in man, thus exposing the conceptus to nickel. Ther is no information at present that nick exposure *in utero* under conditions nickel exposure encountered by pregna women in the U.S. population leads adverse effects.