EVALUATION OF THE HEALTH ASPECTS OF NICKEL
AS A FOOD INGREDIENT

1979

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB

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I. INTRODUCTION

This report concerns the health aspects of using elemental nickel as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1974.* To assure completeness and currency as of the date of this report, this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of April 6, 1979 (44 FR 20797) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of nickel as a food ingredient. The Select Committee received no request for such a hearing.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health.

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*The document (PB-241 972/9) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on nickel and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.
II. BACKGROUND INFORMATION

Nickel is present in the earth's crust and waters, and in the air of urban areas. It constitutes 0.008 percent (80 ppm) of the earth's crust (3). Vanselow (4) reported that soils normally contain 5 to 500 ppm nickel; the average farm soil in the United States contains more than 30 ppm (3).

Nickel is present in seawater in concentrations ranging from 0.1 to 0.5 ppb (3). Nickel has not been identified in most groundwaters; where present, it is found as colloidal nickel. In a summary on the occurrence of trace metals in rivers and lakes of the United States (1962 to 1967), Kopp and Kroner (5) reported nickel in 16 percent of samples analyzed with a mean concentration of 19 ppb. In a report on 969 water supplies in the United States between 1969 and 1974, the average nickel concentration at the tap was 4.8 ppb (3). An adult consuming 2 liters of water per day might ingest 10 μg of nickel. Analyses of 9169 water supplies by the Environmental Protection Agency in the United States between 1969 and 1970 detected nickel in 4977 samples at levels of 1 to 1300 ppb (6). Most nickel in ground and surface waters is due to contamination by man (3).

The level of nickel in seafood ranges from 0.02 ppm in swordfish to 1.70 ppm in salmon (3).

The presence of nickel in soils and waters leads to its incorporation into plants. The nickel concentration of most natural vegetation is between 0.05 and 5 ppm on a dry weight basis (3). It ranges in green vegetables from 0.14 to 1.94 ppm fresh weight; in cereal grains, 0.14 to 2.70 ppm; in potatoes, 0.08 to 0.37 ppm; and in fruits, 0.0 to 1.20 ppm. Its content in milk and milk products is negligible (3,7). The nickel in plants exists in several forms: for example, as cationic nickel and as a negatively charged complex ion (8,9).

Stainless steels, containing 2 to 26 percent nickel, are used extensively in kitchen utensils, tableware, and in equipment for the chemical and food processing industries (10). Depending upon the nature of the alloy and the pH of the food, some nickel may dissolve in the food. For example, Titus et al. (11) cooked 400 g of food for 1 hour in contact with various alloys. The average dissolution of nickel resulted in a concentration of 0.17 ppb.
More than two million pounds of nickel are used in catalytic applications each year. Various compounds may be used in the preparation of the catalyst; e.g., nickelous hydroxide, nickel nitrate and nickel formate, all of which yield finely divided nickel in an active form (10). Raney nickel catalyst is prepared by fusing 50 parts nickel with 50 parts aluminum, pulverizing the alloy and dissolving out most of the aluminum with sodium hydroxide solution. Residual aluminum, which amounts to several percent, appears to be necessary for proper catalytic activity (12). Nickel catalysts are used in the hydrogenation of edible oils and fats. However, most of the metal is removed before packaging. Phatak and Parwardhan (13) state that when nickel is present in finished hydrogenated oils, most is in the form of finely divided metal. They suggest some may be present as nickel soaps formed by the reaction of free fatty acids with metallic nickel in oils that have not been carefully refined before hydrogenation. Postbleaching of oils after hydrogenation by treatment with adsorbent clays to remove traces of nickel is a common practice (14).

The use of nickel-containing alloys implanted in man and animals in a variety of therapeutic prostheses and devices has been reported (15).

Essential roles of nickel have been described for species of livestock, poultry and laboratory animals (16) and it seems probable that this element is also essential or beneficial to man (17). The Food and Nutrition Board of the National Research Council, National Academy of Sciences (18) has stated that the evidence from animal feeding experiments suggests that nickel, as well as tin, vanadium and silicon, are essential, but that their implications for human nutrition are unknown. The World Health Organization in its report on trace elements stated that the range between required and toxic levels of nickel is extremely wide and further that it was not aware of any cases of human toxicity (19).

Nickel is identified by the Food and Drug Administration as unpublished GRAS for use as a catalyst in the hydrogenation of edible vegetable oil. In response to a request from an industrial concern for approval of the use of Rufert nickel catalyst in this application, FDA stated "On the basis of the data which you have presented to us, we would state that it is our opinion that when no more than 0.1 parts per million of nickel is present in the food which is being processed, the Rufert nickel catalyst described would be generally recognized by qualified experts as safe" (20). Presumably, the data submitted with the request showed the presence of no more that 0.1 ppm nickel in the finished hydrogenated oil. Industry has stated more recently that a reasonable range for residual nickel in shortenings and oils might be 0.1 to 1.5 ppm (21) and FDA has requested the Select Committee to evaluate the health aspects of this content of nickel in hydrogenated oils and fats (22).
Nickel is listed by the U.S. Department of Agriculture as a hydrogenation catalyst for animal fats and vegetable oils [9 CFR 318.7] (23). It is also a regulated indirect food additive for use as a component of uncoated or coated food-contact surfaces of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, transporting or holding dry food [21 CFR 176.180] (2). This indirect use is not evaluated in this report.
III. CONSUMER EXPOSURE DATA

No extensive survey of the nickel contents of hydrogenated oils and fats appears to have been made. The panel on nickel, Committee on Medical and Environmental Pollutants, NAS/NRC, stated that the nickel content of hydrogenated oils was generally less than 0.1 ppm (3). Industry response to a FDA request for additional information on selected GRAS substances indicated a weighted mean level of 0.55 ppm nickel in fat and oil products. However, three or fewer companies provided information and the data are not considered statistically significant (24). Assuming that 0.55 ppm nickel was present in all margarine, shortening and edible oils marketed in 1978 (5.2, 8.3 and 9.3 kg per capita, respectively) (25), the per capita intake from these sources would have been about 30 μg per day.

Schroeder et al. (7) calculated the oral intake of nickel from all food and water sources by adult Americans to be 300 to 600 μg per day, and Louria et al. (26) estimated the average oral intake of American adults at 500 μg per day.
IV. BIOLOGICAL STUDIES

Absorption, metabolism, excretion

Nickel may enter the body by at least three routes: oral, in food (7) and water (3); inhalation, from the environment (including tobacco smoke) (7, 26-28); and parenteral, from medications (3), and prostheses and other nickel-containing devices or substances in contact with the skin (15, 27). This report is concerned primarily with the biological effects of elemental nickel and nickel soaps ingested as the result of using nickel as a catalyst in the hydrogenation of edible oils and fats. For comparative purposes, the following discussion includes studies of elemental nickel and nickel compounds administered by routes other than oral, and data on the biological effects of certain nickel compounds.

Labeled nickel administered intraperitoneally as $^{63}$NiCl$_2$ (1 $\mu$Ci or 102 $\mu$g Ni$^{++}$), was reported by Wase et al. (29) to be distributed in all tissues of C57B1/6 mice with the highest concentration in kidney, lung, and plasma. The slowest clearance was from the lungs and brain; the lungs retained 38.6 percent of uptake after 72 hours, the brain 16.7 percent. Most of the nickel was excreted via the feces in the first 8 hours; urinary excretion was maximal during the first 4 hours. Selivanova et al. (30) dispersed finely divided nickel (0.19 $\mu$m in diameter) in distilled water and administered it intravenously to mice, rats and rabbits and orally to mice and rats in doses ranging from 10 to 600 mg per kg body weight daily for 5 days. Nickel sulfate, nickel carbonate and nickel nitrate were also administered intravenously. Metallic nickel was reported to have cumulative properties whereas the salts did not. Metallic nickel (as administered) accumulated in the lungs, liver, spleen and kidneys; six days after administration the lungs retained the highest concentration. Most of the ingested nickel was not absorbed and was excreted in the feces; some was excreted in the urine. It has been suggested that a mechanism exists limiting the absorption of nickel (7).

Schroeder et al. (7) reported that there is approximately 10 mg of nickel in a normal man. Perry and colleagues (31) analyzed tissues (liver, kidney, lung, aorta, heart, spleen and brain) taken at autopsy from 150 American subjects. Concentrations in each tissue ranged widely among individuals; highest concentrations of nickel were found in the lungs, heart and aorta. Nickel has also been reported in human intestine, skin, trachea and larynx (7); sweat (32); milk (33); synovial fluid (34); and fetal tissues (7).
The levels in serum and urine reflect environmental exposure to nickel. For example, McNeely et al. (35) reported mean serum levels of 2.6 μg per liter and urinary excretion of 2.5 μg per day in healthy adult residents of Hartford, Connecticut, an area of low environmental nickel concentration. In Sudbury, Ontario, Canada, a city with high environmental concentrations of nickel, mean serum levels were 4.6 μg per liter and urinary excretion was 7.9 μg per day.

Sunderman (36) reported that nickel is present in three forms in serum: ultrafilterable, albumin-bound, and the metalloprotein, nickeloplasmin. Serum nickel levels for man, rat, dog and rabbit were 2.3, 6.6, 2.3, and 9.0 μg per liter, respectively (37). The level for man compares favorably with that reported by McNeely et al. (35). The percentages of the total nickel present in the ultrafilterable form in these species were 41, 17, 85, and 16 percent, respectively (37).

Horak and Sunderman (38) found that the mean fecal excretion of nickel by ten subjects both male and female, 22 to 65 years of age, who were ingesting normal diets, was 3.3 μg per g wet weight (14.2 μg per g dry weight), amounting to 258 μg per day. They reported that fecal excretion was 100 times greater than the average urinary excretion (2.6 μg per day) of 50 comparable subjects.

Nodiya (39) reported that ten male students, 17 years of age, who ingested 289 μg nickel per day excreted 258 μg nickel per day in the feces and 29 μg in the urine. This represented 10 percent absorption of the nickel ingested.

**Acute toxicity**

Metallic nickel and insoluble nickel salts, when administered orally to animals, have relatively low toxicities (30). They are more toxic when injected parenterally.

Dogs tolerated single oral doses of 1 to 3 g of metallic nickel per kg body weight without observable adverse effects (40). Large doses of nickel salts administered orally to experimental animals caused gastrointestinal irritation, vomiting and diarrhea. Acute oral LD values for nickel, nickel chloride, and nickel sulfate are presented in Table I. For comparison, lethal doses as determined by other routes of administration are included.

**Short-term studies**

Schroeder (45) added 5 ppm nickel acetate to the drinking water of rats. Dietary content of nickel was 0.44 ppm and the estimated total daily intake of nickel was 375 μg per kg of body


<table>
<thead>
<tr>
<th>Substance</th>
<th>Species</th>
<th>Sex and No.</th>
<th>Route</th>
<th>Measurement</th>
<th>Dosage as Ni mg/kg</th>
<th>Reference</th>
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<tbody>
<tr>
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<td></td>
<td></td>
<td>Female 2</td>
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<tr>
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<td></td>
<td>LD₁₀₀</td>
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<td>(3 to 5 days)</td>
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<td>30</td>
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<td></td>
<td>LD₁₀₀</td>
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<td>p.o.</td>
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<td>i.v. (repeated injection)</td>
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<td>30</td>
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<td></td>
<td></td>
<td>LD₁₀₀</td>
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<tr>
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<td>s.c.</td>
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<td>(immediate)</td>
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**TABLE I**

Acute Toxicity of Nickel and Nickel Compounds
weight. The rats were exposed from weaning until 11 months of age. Serum cholesterol level was lower in both males and females that received the nickel salt than in controls (75 vs 123 mg per 100 ml for males, and 75 vs 95 mg per 100 ml for females).

Itska et al. (41) administered solutions of nickel chloride daily to groups of 12 rats by stomach tube for 7 months at levels of 0.0005, 0.005, 0.05, 0.5, and 5.0 mg nickel per kg body weight. Doses of 5.0 mg per kg caused a statistically significant decrease in the absorption of calcium and magnesium, a lesser weight gain, and a decrease in the concentration of ascorbic acid in the liver as compared to control animals.

Tardivel et al. (46) administered pulverized nickel orally to rabbits at doses of 5 to 20 mg per kg daily or powdered nickel at doses of 100 to 500 mg per kg daily for a period of 9 months. There were no deaths. Treated animals demonstrated leukocytosis and changes in the electrophoretic pattern of the serum globulins.

Metallic nickel was administered orally to cats and dogs at levels of 4 to 12 mg nickel per kg body weight daily for 200 days without observable evidence of adverse effects (40).

Nickel carbonate, nickel soaps of peanut oil fatty acids, or nickel catalyst was added to diets of adult monkeys (Macacus sinicus) at levels of 250, 500, and 1000 ppm nickel equivalent (13). No effect on the general health, blood cell count, or hemoglobin level was observed after feeding these diets for 24 weeks.

Male and female Swiss-Webster mice were fed diets containing 1100 and 1600 ppm nickel (about 210 and 335 mg nickel per kg body weight) as nickel acetate for 4 weeks (47). Weight gains of males were significantly depressed at the higher dietary level; both levels of added nickel resulted in significant decreases in weight gains in females. Although litter size was not significantly affected, females fed diets containing 1600 ppm nickel weaned significantly fewer pups than those fed the control diet.

To investigate its effects on growth and reproduction of rats, nickel was added to their diets in the form of nickel catalyst, nickel soaps of peanut oil fatty acids, and nickel carbonate at levels of 250, 500, and 1000 ppm nickel (about 25, 50 and 100 mg per kg body weight) (13). After 8 weeks, weight gains were least for groups fed the highest dietary level of all forms of nickel but did not differ significantly from that of the control animals. A 4-day balance study showed that approximately 74 to 90 percent of the nickel was excreted in the feces and 1.6 percent in the urine. There were no significant effects on reproductive performance.
Subcutaneous administration of nickel sulfate to rats at a dose of 0.04 mmol/kg (about 2.3 mg nickel per kg) resulted in marked testicular effects including shrinkage of central tubules, hyperemia, and degeneration of spermatozoa which were reversible (48). Oral administration of nickel sulfate at doses of 25 mg (9.4 mg nickel) per kg body weight for 120 days resulted in inhibition of spermatogenesis and infertility (49).

Long-Evans BLU:LE) rats were born and bred in a trace-metal-free environment and were given 5 ppm nickel as a soluble salt in their drinking water (about 350 µg per kg body weight daily) (50). Three generations (10 to 15 litters per generation) were studied. Rats were allowed to breed up to 9 months of age or more. The size of litters decreased somewhat with each generation, fewer males were born in the third generation and the percentage of young deaths was significantly greater than that of controls in each generation.

In a three-generation reproduction study, groups of Wistar rats were fed diets containing 25, 50, or 1000 ppm nickel (about 25, 50 or 100 mg nickel per kg) as nickel sulfate (51). Twenty pairs from the F/0, F/1b, and F/2b generations were mated at 13 weeks of age. Following weaning of the second litters of each generation, surviving parents (maximum life, 37 weeks) from each diet level were sacrificed and necropsied. No adverse effects were noted on fertility, gestation, viability and lactation at any dietary level of nickel. A higher incidence of stillborns was observed only in the F/1a litters at all dietary levels of nickel. Histopathological studies performed on ten male and ten female F/3b weanlings at each diet level revealed no lesions.

Parenterally administered nickel and nickel salts have been reported to elicit central nervous system responses in animals. For example, the intraperitoneal administration of nickel chloride (30 mg nickel per kg) to rats has been reported to cause a breakdown in the blood-brain barrier (52). Metallic nickel spheroid pellets (3 to 5 mm in diameter) implanted in the cortex of the monkey elicited epileptic seizures (53). At necropsy, the pellets were surrounded by necrotic soft tissue.

Long-term studies

White Charles River CD weanling mice (50 males and 54 females) were given 5 ppm nickel (as nickel acetate) in their drinking water (about 375 µg nickel per kg) (54). The level of nickel in the kidneys was increased over the control levels. There were no effects on mean body weights, mortality or incidence of tumors.

Groups of Long-Evans BLU:LE) rats (52 of each sex) were fed a diet containing the following metals in ppm: nickel, 0.44; molybdenum, 0.25; cadmium, 0.07; zinc, 22.3; copper, 1.36; mangan-
nese, 12.7; chromium, 0.14 and cobalt, 0.41 (55). Treated rats were given drinking water that contained 5 ppm nickel as nickel acetate. Estimated total dietary intake of nickel by adult rats was about 375 μg per kg body weight. No increase in nickel was found in spleen, heart, lung or liver; concentration tended to be higher in the kidneys but the increase was not significant (P=0.05). However, feeding of nickel was associated with increased concentrations of chromium in heart and spleen and manganese in kidney, and with reduced copper in lung and spleen, zinc in lung and manganese in spleen (P<0.05). The duration of exposure was 36 months. Life span was not affected but treated animals experienced a lesser weight gain. Incidence of tumors was not affected.

Forty-two young rats (4 to 5 weeks old) were fed a diet containing 25 mg nickel (about 15 mg per kg body weight) in the form of nickel catalyst per 100 g diet for a period of 16 months (56). Nickel accumulated in soft tissues and bones reaching maximum values at 8 months after which a decline occurred. Balance studies indicated that diminished absorption of nickel was probably the reason for the decline in tissue nickel. There was no adverse effect on growth or general health. When the protein content of the diet was reduced from 16.4 to 6.8 percent, the level of nickel in all tissues was reduced. Nickel was eliminated from the body after it was removed from the diet. Thirty to 40 days after termination of the diet, urine and feces were nickel-free.

Weanling Wistar rats in groups of 25 of each sex were fed diets containing 100, 1000, and 2500 ppm nickel (about 5, 50 and 125 mg per kg body weight for adult rats) as nickel sulfate for 2 years (51). Weight gains were significantly reduced in females that received diets containing 1000 and 2500 ppm nickel and in males fed the latter diet. Hematologic values for hemoglobin, hematocrit, and differential leukocyte counts obtained at 3-month intervals did not differ significantly from controls for any treated group. Gross pathologic findings at necropsy were negative. Histologic findings were essentially negative. The distribution of lesions was not related to treatment.

Groups of 6-month-old beagles (three of each sex) were fed diets providing 100, 1000, and 2500 ppm nickel (about 2.5, 25, and 63 mg per kg body weight) for 2 years (51). Weight gains were depressed at the highest treatment level but food consumption was comparable with that of controls and the other treated groups. Tissue analysis at necropsy showed a significant increase in nickel retention only in the kidneys (7.8 ppm vs 5.7 ppm in controls) and livers (33 ppm vs 28 ppm in controls) in dogs receiving 2500 ppm nickel in their diet. Kidney and liver organ-to-body weight ratios were also significantly higher in this treatment.
group. Microscopic examination of tissues showed no characteristic lesions in the groups fed diets containing 100 or 1000 ppm nickel. All dogs in the 2500 ppm treatment group showed histologic changes in their lungs: subpleural peripheral cholesterol granulomas in five dogs, bronchiolectasis in four, emphysema in three, and "focal cholesterol pneumonia" in four. Granulocytic hyperplasia of the bone marrow was observed in two dogs that were fed 2500 ppm nickel in their diet.

Special studies

Interaction with enzymes. Nickel is both an activator and an inhibitor of enzymatic activity but it is not known to be an intrinsic component of any enzyme.

Nickel ion can activate arginase (57), enolase (58), phosphoglucomutase (59,60), ATP-ase (61), and ribulose diphosphate carboxylase (62). Nickel can replace zinc in carboxypeptidase (63,64) and in carbonic anhydrase, but the latter complex has no hydration or esterase activity (65). The following enzymes are inhibited by nickel salts: dialkylfluorophosphatase (66), RNA polymerase (67), 5'-nucleotidase and human bone alkaline phosphatase (68), cytochrome C reductase, cytochrome oxidase, malic dehydrogenase, and isocitric dehydrogenase (50).

Dermatitis. Contact with nickel or solutions of nickel salts may result in dermatitis (3,15,27). Dermatitis from contact with nickel-plated articles, jewelry and coins has been known for some time and numerous cases have been reported among workers in nickel electroplating firms and in nickel refineries (27). The Select Committee is not aware of data concerning the incidence of allergic responses to orally ingested nickel or nickel salts.

Carcinogenicity. Many experimental systems have been employed in the study of nickel carcinogenesis in animals. The carcinogenic effect of nickel following parenteral administration or inhalation appears to be well documented (3). The Select Committee is aware of no evidence that nickel or nickel salts administered orally are carcinogenic.

Sunderman (69) in a review of nickel carcinogenesis reported that more than 327 cases of lung cancer and 115 cases of nasal cancer have been documented among workers who were occupationally exposed to inhalation of nickel compounds. Possible carcinogenic agents involved have been considered to be respirable particles of metallic nickel, nickel sulfides, nickel oxides and vapors of nickel carbonyl. Epidemiological studies in several
countries, including England and Canada, have demonstrated a significantly greater incidence of cancers of the respiratory tract among nickel refinery workers than among the general population. Doll (70) and Morgan (71) reported greater incidence of lung cancer (5-fold) and nasal cancer (150-fold) among Welsh nickel workers during the period of 1948-1956. However, Doll et al. (72) have reported more recently that incidence of lung and nasal cancer was greatly reduced in workers who began their employment after 1925 when modifications in the refining process were made and changes in the composition of the raw material occurred.

In a series of experiments designed to evaluate the carcinogenicity of metallic nickel, Hueper (73,74) administered suspensions of finely divided nickel powders via various routes (subcutaneous, intranasal, intrapleural, intrafemoral) to Osborne-Mendel and Wistar rats. Sarcomas affecting bones, connective tissue and muscle were produced. It was concluded that finely dispersed metallic nickel may elicit cancerous reactions in tissues contacted. Exposure of rats and guinea pigs to atmospheres containing 15 mg nickel (4 μm diameter or less) per cubic meter for 6 hours daily, 4 or 5 days each week, for 21 months resulted in benign and malignant pulmonary neoplasms (75). The intramuscular administration of powdered nickel (0.5 to 0.8 μm particles in aggregates 3 to 117 μm in longest dimension) has been reported to produce tumors of the striated muscle of rats (76,77). The generalization that the more soluble the nickel compound the greater its toxicity and the less its carcinogenicity was supported by the findings of Gilman (78) and Payne (79) who compared the carcinogenicity of intramuscular implants of nickel sulfide, carbonate, oxide, chloride, anhydrous acetate, acetate and sulfate among other salts. The carcinogenicity of inhaled nickel carbonyl has been well documented (3,80,81).

Mutagenicity and teratogenicity. The Select Committee is not aware of any studies that have been made of the possible teratogenic or mutagenic effects of orally administered nickel or nickel compounds.
V. OPINION

This opinion concerns the only GRAS use of nickel, that as a catalyst in the hydrogenation of edible oils and fats. According to industry, a residue of 0.1 to 1.5 ppm nickel may be present in the hydrogenated oils. There are few data on the amount of nickel actually consumed by humans from this source, but at the average level of 0.55 ppm reported by industry in 1975 it can be estimated that the per capita daily intake from the residual in hydrogenated oils was about 30 μg. This amount is about an order of magnitude lower than that ingested in the diet from natural sources, which is estimated at 300 to 600 μg per day.

Most of the nickel ingested is excreted in the feces; a small proportion is absorbed and excreted in urine and sweat. Nickel and nickel salts when administered orally to various species of animals have relatively low toxicities. Granulocytic hyperplasia of the bone marrow was observed in dogs fed high levels (60 mg per kg body weight) of nickel as the sulfate but carcinogenicity has not been reported for nickel and nickel salts administered orally to experimental animals; however, tumors have resulted following parenteral administration. Adverse effects on reproductive performance have been reported in mice fed nickel acetate; daily intake of nickel was estimated to be 335 mg per kg body weight. Daily ingestion of 9.4 mg nickel as nickel sulfate per kg body weight, has caused infertility in rats. However, no effect on the reproductive performance of rats resulted from feeding up to 100 mg per kg body weight of catalytic nickel powder. The existence of nickel dermatitis from occupational contact with nickel or nickel salts as well as in the general population is recognized. No data are available indicating the occurrence of allergic reactions to the oral ingestion of nickel and nickel salts.

Based on these considerations, the Select Committee concludes that:

There is no evidence in the available information on elemental nickel that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced or that might reasonably be expected in the future.
VI. REFERENCES CITED


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