American Contact Dermatitis Society

President
Donald V. Belsito, M.D.
4023 Wescoe Pavillion
KUMC
3901 Rainbow Blvd.
Kansas City, KS 66160

President-Elect
James G. Marks, Jr., M.D.
Milton S. Hershey Medical Ctr.
P.O. Box 850, MCHU14
Hershey, PA 17033-0850

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Henry Ford Hospital
Dermatology Clinic
2799 West Grand Blvd.
Detroit, MI 48202

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34 Ashfield Road
Atherton, CA 94027

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555 Laurel Avenue
Apartment 108
San Mateo, CA 94401

May 24, 2000

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens, MD EC-14
P.O.Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson:

As President of the American Contact Dermatitis Society, I would like to respond to the recent announcement in the Federal Register that the National Toxicology Program is proposing the addition of nickel to their Report on Carcinogens. Human exposure to nickel is common, given its widespread use in industry and in consumer products. Historically, the heaviest exposures to nickel have occurred in the workplace, in environmental settings proximate to industrial sources, or from consumer goods that directly contact cutaneous / mucosal surfaces.

Experimental and epidemiological data have shown that sparingly soluble nickel compounds, and possibly also the soluble compounds, are carcinogens linked to lung and nasal cancers in humans (R.B. Hayes. The Carcinogenicity of Metals in Humans. *Cancer Causes Control* 1997; 8:371-385). The presumed route of exposure for carcinogenesis has been inhalation (C.F. Kuper, et al. Carcinogenic Response of the Nasal Cavity to Inhaled Chemical Mixtures. *Mutat Res* 1997; 380:19-26); however, recently, exposures from medical and dental devices have been scrutinized (C.G. Lewis and F.W. Sunderman, Jr. Metal Carcinogenesis in Total Joint Arthroplasty -- Animal Models. *Clin Orthop* 1996; 329(suppl):S264-8; S.J. Newsholme and D.M. Zimmerman. Immunohistochemical Evaluation of Chemically Induced Rhabdomyosarcomas in Rats: Diagnostic Utility of MyoD1. *Toxicol Pathol* 1997; 25:470-4; and, J.C. Wataha. Biocompatibility of Dental Casting Alloys: A Review. *J Prosthet Dent* 2000; 83:223-34). Furthermore, it has been hypothesized that certain paternal exposures to metals might increase the risk of cancer in progeny (R. Liang, et al. Effects of Ni (II) and Cu (II) on DNA Interaction with the N-Terminal Sequence of Human

Protamine P2: Enhancement of Binding and Mediation of Oxidative DNA Strand Scission and Base Damage. *Carcinogenesis* 1999; 20:893-8).

The mechanism by which nickel induces carcinogenicity is unclear. Among the possibilities include: 1) tumor induction by direct or indirect actions of nickel compounds on DNA (genetic or epigenetic, heritable changes); 2) co-carcinogenicity by deregulating cellular proliferation; and/or 3) tumor promotion. As reviewed by A.R. Oller, et al. (Carcinogenicity Assessment of Select Nickel Compounds. *Toxicol Appl Pharmacol* 1997; 143:152-166), different risk assessments need to be done for compounds that might produce cancer by genetic/epigenetic mechanisms (e.g., nickel subsulfide), compounds that could act as co-carcinogens (e.g., nickel oxide), and compounds that may act as tumor promoters (e.g., nickel sulfate). I trust that you will consider these matters in designing your NTP studies. Furthermore, as a dermatologist, I would like to alert you to the significant morbidity (although not mortality) that our patients experience from their exposure to nickel: allergic contact dermatitis.

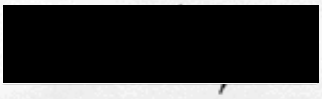
When last evaluated in the United States more than two decades ago, the point prevalence of allergic reactions to nickel among the general population was approximately 10% (S.D. Prystowsky, et al. Allergic Contact Hypersensitivity to Nickel, Neomycin, Ethylenediamine and Benzocaine: Relationships Between Age, Sex, History of Exposure, and Reactivity to Standard Patch Tests and Use Tests in a General Population. *Arch Dermatol* 1979; 115:959-62). However, it should be pointed out that the incidence of nickel allergy in the general population has increased significantly since that time. Thus, in a recent study from Norway, approximately 30% of women in two different regional areas were noted to be allergic to nickel, while the incidence rate among men was approximately 5% (T. Smith-Sivertsen, et al. Nickel Allergy in its Relationship with Local Nickel Pollution, Ear Piercing, and Atopic Dermatitis: A Population-Based Study From Norway. *J Am Acad Dermatol* 1999; 40:726-35). The difference in the incidence rates of nickel allergy between men and women has been postulated to be largely due to body piercing, a practice which has become much more prevalent worldwide.

Because of the increasing rate of nickel sensitization, Denmark passed a statutory order in 1991 (Danish Ministry of Environment. Statutory Order of the Danish Ministry of Environment Regarding Prohibition of Sale and Labeling of Certain Nickel Releasing Objects. Statutory Order #854 of 16 December 1991), which limited the permissible release of nickel from metal objects intended for close contact with the skin (e.g., earrings, eyeglass frames, buttons, etc) to $\leq$ 0.5 $\mu g/cm^2$ of skin per week. This level was based upon a number of studies that indicated the relative lack of sensitization to nickel in concentrations at or below $\mu g/cm^2$ of skin per week. In follow-up studies by J.D. Johansen, et al (Changes in the Pattern of Sensitization to Common Contact Allergens in Denmark Between 1985 - 86 and 1997 - 98, with a Special View to the Effect of Preventive Strategies. *Br J Dermatol* 2000; 142:1490-5), it was found that the frequency of nickel allergy among children (0 to 18 years of age) decreased from a high of 24.8% prior to the enactment of the above referenced legislation to 9.2% thereafter. Shortly, the EEC will be enacting the Directives of the European Standards for the

Analytical Methods to be used on the Nickel Directive, which was initially reviewed in 1994 (94/27/EEC, 12th Amendment of Directive 76/769/EEC). Briefly, this directive states that nickel should **not** be used in earring post assemblies at concentrations $\geq$ 0.05%; in products intended to come into direct and prolonged contact with the skin at concentrations $\geq$ 0.5 $\mu g/cm^2$ of skin per week; or, in coated products, designed to come into direct and prolonged contact with the skin, that would release $\geq$ 0.5 $\mu g/cm^2$ of skin per week of nickel after two years of normal use (C. Lidén, et al. Nickel-Containing Alloys and Platings and Their Ability to Cause Dermatitis. *Br J Dermatol* 1996; 134:193-8). Although these laws are intended to prevent the induction of new cases of nickel allergy, they unfortunately will not benefit a significant number of patients already sensitized to nickel, who have been found to react to such low concentrations of aqueous nickel salts as 10 ppm (N.H. Nielsen, et al. Effects of Repeated Skin Exposure to Low Nickel Concentrations: A Model for Allergic Contact Dermatitis to Nickel on the Hands. *Br J Dermatol* 1999; 141:676-82). Nonetheless, I would request that the National Toxicology Program consider restricting nickel exposure to the above referenced European limits when performing risk assessments for carcinogenicity. Of course, should the carcinogenic doses prove to be lower than above, further restrictions would be in order.

In summary, whether exposure to nickel is or is not found to represent a significant risk for carcinogenesis, as the President of the American Contact Dermatitis Society, I would ask that regulatory authorities in the United States follow the lead of those in the EEC by restricting consumer exposure to nickel at: 1) $\leq$ 0.5 $\mu g/cm^2$ of skin per week for all products intended to come in direct and prolonged contact with the skin: and, 2) $\leq$ 0.05% for products intended for exposure to non-epithelialized skin (e.g., post-assemblies used during ear piercing) or mucosa (e.g., dental devices), as well as for devices inserted within the body (e.g., orthopedic devices). If I can be of further help in your deliberations on this matter, please do not hesitate to contact me.

Sincerely,



Donald V. Belsito, M.D.
Director, Division of Dermatology
University of Kansas Medical Center
President, American Contact Dermatitis Society
President, North American Contact Dermatitis Group

Enclosures:

S.D. Prystowsky, et al. Allergic Contact Hypersensitivity to Nickel, Neomycin, Ethylenediamine and Benzocaine: Relationships Between Age, Sex, History of Exposure, and Reactivity to Standard Patch Tests and Use Tests in a General Population. *Arch Dermatol* 1979; 115:959-62

T. Smith-Sivertsen, et al. Nickel Allergy in its Relationship with Local Nickel Pollution, Ear Piercing, and Atopic Dermatitis: A Population-Based Study From Norway. *J Am Acad Dermatol* 1999; 40:726-35

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N.H. Nielsen, et al. Effects of Repeated Skin Exposure to Low Nickel Concentrations: A Model for Allergic Contact Dermatitis to Nickel on the Hands. *Br J Dermatol* 1999; 141:676-82