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

June 20, 2000

Dear Dr. Jameson:

The American Academy of Dermatology [hereinafter referred to as "the Academy] submits these comments in response to the National Toxicology Program's recommendations to list ultraviolet radiation (UVR), nickel and nickel compounds, and human papillomaviruses (HPVs) in its tenth edition of the "Report on Carcinogens." The Academy supports the NTP's recommendations of inclusion of these materials on its list of known or suspected carcinogens.

Ultraviolet Radiation

Solar exposure is an environmental issue with profound effects for the majority of Americans. In this century, changes in attitudes of most Americans toward fashion and beauty as well as an increase in leisure activity outdoors has cost us dearly in terms of photodamage, photoaging, and photocarcinogenesis. In the last decade, however, public health education programs have been initiated to try to convince the American public of the error of its ways. This has been a public/private partnership with such entities as the Environmental Protection Agency, the National Institutes of Health, the Centers for Disease Control and Prevention, the American Academy of Dermatology, the American Cancer Society, The Skin Cancer Foundation and others providing educational materials in a variety of formats and media. We believe that adding UVR to the list of known carcinogens would be of great importance to our efforts to convince the public that unprotected sun exposure is dangerous and may lead to the development of melanoma and non-melanoma skin cancers, such as basal cell and squamous cell carcinoma.

This year, the American Academy of Dermatology estimates that 1.3 million Americans will be diagnosed with some form of skin cancer. The causal agent for the majority of these skin cancers is exposure to UVR. Genetic damage from UVR occurs in two general forms, mutations and chromosome damage. Both are important to the development of the majority of neoplasms seen on the skin – both benign and malignant lesions. Exposure to UVR leads to mutations in the DNA by at least two potential mechanisms. In general, mutations arise in the skin when UV-induced covalent damage is misrepaired, altering the base sequence from the original. Alternatively, undetected covalent damage that is not repaired prior to DNA replication could induce a misread by DNA polymerase, causing a base substitution that alters the original sequence.

Pyrimidine dimers and 6-4 photoproducts are two of the most important classes of direct DNA damage induced by UV. The peak wavelength for the formation of pyrimidine dimers and 6-4 photoproducts is 300 nm, so it is more than likely that UVB radiation is the major source of mutations in the human skin. In addition, most of the mutations seen in the p53 gene, an important tumor suppressor gene in human skin cancer are C→T and C→TT transitions. This is consistent with UVB-induced pyrimidine dimer formation as the initial effect. While UVB radiation can induce DNA damage directly through the formation of photoproducts, *in vitro* studies have shown that UVA requires an intermediate molecular target to generate the reactive oxygen species that are thought to be the primary mediators of UVA-induced damage.

UVB and UVA radiation can induce DNA damage indirectly, through the generation of reactive oxygen species, also known as free radicals. Products such as superoxide, singlet oxygen, hydrogen peroxide and hydroxyl radials – all generate from UV striking molecular targets in cells – can introduce DNA adducts or other covalent changes in the DNA. When covalent changes are unrecognized or unrepaired, they may be misread at the time of DNA replication prior to cell division, leading to permanent mutations in the DNA base sequences.

A characteristic change in DNA due to oxidative effects of UV radiation is the formation of 8-hydroxyguanine, a derivative of the purine base deoxyguanine. Base modifications characteristic of oxidative damage are produced by wavelengths throughout the UVA and UVB spectra, although the yield of pyrimidine dimers decreases exponentially above 315 nm – near the transition from UVB to UVA. In addition, there is a second peak of oxidative damage that occurs in the visible range between 400 and 450 nm. This suggests that blue light may also contribute to DNA damage. Support for the possibility that visible light may contribute to carcinogenesis comes from a fish model of melanoma, in which wavelengths in this range can trigger tumor development. More research, however, is needed in this area.

UV-induced chromosome damage is less well understood than UV-induced mutations, although there is abundant evidence that this is a major pathway for tumorigenesis. Chromosome translocations can inactivate tumor suppressor genes or up-regulate tumorigenic oncogenes. Non-random chromosome deletions are an important means of inactivation of function for tumor suppression genes, as control gene function is lost when a germ line defect combines with a somatic event or when two somatic events occur in both alleles.

In addition to skin cancers, there is strong epidemiological evidence linking UVR exposure to other malignancies. Data from the Swedish cancer registry indicates that UVR exposure may be an etiologic factor in non-Hodgkin's lymphoma. Much more research needs to be done in this area, but if these epidemiological observations are true, UVR may be a far more significant carcinogen than is currently appreciated.

Exposure to UVR has other deleterious health effects. Many of the cutaneous changes that we associate with aging are due primarily to exposure to UVR, and therefore are potentially preventable. Animal models have shown that both UVA and UVB contribute to photoaging. These cutaneous changes are caused by oxidative damage and stress, such as lipid peroxidation, as well as erythema. UVR effect on cytokine release and signal transduction pathways may alter the expression of enzymes that remodel the dermis. A photoaging-related effect of chronic exposure to UVR is solar elastosis, or the presence of abnormal elastin in the skin. Metalloproteinases, such as collagenase, can be up-regulated by UVB exposures equivalent to 1/6 of the minimal dose of UVB that produces erythema; this effect contributes to the development of cutaneous photoaging.

There are also a number of photosensitive disorders in which UVR plays a significant role. The two most studied are polymorphous light eruption (PMLE) and lupus erythematosis. PMLE is characterized by pruritic inflammatory skin eruptions seen primarily on the arms and upper trunk. PMLE is a relatively common disorder, affecting 10% of the general population. Individuals of Native American and Scandinavian ancestry are more at risk for these abnormal reactions to sunlight.

Lupus erythematosis is an autoimmune disorder characterized by the presence of inappropriate antibodies to self-antigens. Autoantibodies to DNA are highly characteristic of the disease. As with PMLE, UVB and UVA and perhaps visible light can play a role in the induction of lupus. This suggests that oxidative damage may play an important role in the disorder. Photosensitivity is a common manifestation of several forms of lupus, and tends to correlate with a less favorable prognosis and more organ involvement in systemic lupus and exacerbations of cutaneous lupus.

Nickel and Nickel Compounds

The Academy joins with our colleagues in the American Contact Dermatitis Society in supporting efforts that would reduce human exposure to nickel and nickel compounds. We ask that the NTP follow the lead of our European counterparts to reduce occupational and consumer exposure to nickel.

Currently, human exposure to nickel is common, as it is used widely in both industry and in consumer products. Experimental and epidemiological data have shown that sparingly soluble nickel compounds, and possibly also the soluble compounds, are carcinogenic in humans. Exposure to these metals has been linked to the development of lung and nasal cancers. The presumed route of exposure for carcinogenesis has been inhalation, although recently exposures from medical and dental devices have also been scrutinized. Furthermore, it has been hypothesized that certain paternal exposures to nickel may increase the risk of cancer in progeny. The mechanism by which nickel induces carcinogenicity, however, still remains unclear, but may be caused by direct or indirect actions of nickel compounds on DNA, co-carcinogenicity by deregulating cellular proliferation, and/or tumor promotion. Much more research needs to be undertaken to determine which compounds are co-carcinogens and which act as tumor promoters.

In addition to its possible links to cancer, exposure to nickel causes another health effect of considerable morbidity – allergic contact dermatitis. Twenty years ago, epidemiological evidence showed that nearly 10% of the US population exhibited some sensitivity to nickel. Since that time, the incidence of nickel allergy has increased dramatically. In a recent study published in Norway, approximately 30% of women in two different regions of that country were found to be allergic to nickel, while the incidence rate among men was approximately 5%. Scientists postulate that gender differences in the incidence rates of nickel allergy maybe due primarily to the common practice of body piercing.

Because of the increasing rate of nickel sensitization, the Danish Ministry of the Environment recently issued a statutory order limiting the permissible release of nickel from objects intended for close contact with the skin to $\leq 0.5\ \mu g/cm^2$. These items include earrings, eyeglass frames, and buttons. This level was based on a number of studies that indicated the relative lack of sensitization to nickel at concentrations at or below $0.5\ \mu g/cm^2$ per week. Since the adoption of these nickel restrictions, the frequency of nickel allergy among children decreased from a high of 24.8% prior to the enactment of the new standard to 9.2%.

Shortly, the European Community will enact the *Directives of the European Standards for the Analytical Methods* to be used on the nickel directive. This directive states that objects, which come into direct and prolonged contact with the skin, must not contain more than $0.5\ \mu g/cm^2$ of nickel. Although this new law will prevent new cases of nickel sensitization, it will unfortunately have little effect on those individuals already sensitive to the metal. However, given the growing incidence of nickel allergy, prevention is very important and I would urge that the NTP consider restricting nickel exposure through the adoption of the European standard.

Human Papillomaviruses

The Academy supports the listing Human papillomavirus (HPV) as a known human carcinogen. Historically, dermatologists have played a crucial role in the diagnosis and treatment of sexually transmitted diseases (STDs), because many of these infections present predominantly with cutaneous signs and symptoms. Given our experience in vast experience in treating this prevalent viral STD, it is our expert opinion that listing HPV as a known carcinogen will assist us in our efforts to educate the general public about the dangers of this disease, how it may be prevented, how it is diagnosed, and how it is treated.

There are over 70 distinct types of HPV. Nearly half, 30 types, are transmitted sexually by skin-to-skin contact and cause genital HPV. According to the American Social Health Association, 5.5 million new cases of sexually transmitted HPV occur each year, and 20 million Americans are thought to have an active HPV infection at any given time. This year, direct annual medical costs for treating the symptoms of HPV infection is expected to reach $6 billion.

While many forms of the virus are harmless, certain strains of HPV have been clearly linked to the development of cervical lesions and then to cervical cancers. Indeed, over 99% of cervical cancers are associated with HPV. Cervical cancer is the second most common cacer of women in the world. In 1999, 500,000 women in the United States were diagnosed with cervical cancer, and 200,000 died from it. As with skin cancers, the lag time between exposure and the development of the cervical cancer is often lengthy, sometimes between 10 and 20 years. In addition to cervical cancers, exposure to certain strains of HPV is linked to the development of other cancers such as carcinomas of the nasal septum, laryngeal and hypopharyngeal carcinoma, cancers of the upper digestive and respiratory tract, as well as other anogenital cancers.

Unfortunately, the majority of Americans are unaware of the linkage between certain strains of HPV and cervical and other cancers. According to an expert panel convened in 1999 by the Centers for Disease Control and Prevention, many health care providers were equally unaware of the risks of exposure to HPV and the development of cervical cancer as well as to the new screening techniques for HPV and treatment modalities for cervical cancer.

Listing HPV as a known carcinogen will bring a clarity to our public health messages concerning HPV. It will provide an impetus to clinicians to learn more about the dangers of this viral STD and will encourage those at risk to be tested.

In summary, the Academy supports the listing of UVR, nickel and nickel compounds, and HPV to the NTP's tenth edition of the "Report on Carcinogens." A comprehensive list of citations from peer-reviewed clinical journals and Academy reports is appended to this letter. If I can be of further assistance to you in your deliberations, please do not hesitate to contact me.

Sincerely,

[redacted]

Richard Scher, M.D.
President

**PLEASE NOTE: Human Papillomavirus is being deferred for review until the 2001 review cycle.

Report on Carcinogens Group, NIEHS/NTP

Citations – UV Radiation

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