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What Is the Role of Thiurams in Allergy to Natural Rubber Latex Products?

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Thiurams, which function as accelerators in the vulcanization of rubber, are allergens capable of causing allergic contact dermatitis (ACD) in susceptible individuals.[1] Initial cases of thiuram sensitivity occurred during the 1920s, when eczematous reactions were reported in rubber industry workers.[2] During the 1930s, as the agricultural industry started using thiuram-based chemicals as germicides and fungicides on farmlands, lawns, and golf courses, thiuram allergy was noted in dock laborers unloading bananas, as well as in golfers, gardeners, and florists.[3] An increased incidence in thiuram-related allergy became evident in health care workers during the 1990s, related to the widespread use of natural rubber latex (NRL) gloves in health care facilities as they complied with Universal Precautions, outlined by the Occupational Safety and Health Administration's Blood Borne Pathogen Standard. In 2001, it was estimated that 33% of health care workers suffered from thiuram-related hand dermatitis.[4]

Natural rubber latex is derived from the milky sap of the commercial rubber tree, *Hevea brasiliensis*, and is used in the production of NRL products both within the health care environment (eg, gloves, catheters, skin adhesives) and without (eg, balls, sealants, pacifiers). The sap from this tree is a complex mixture of protein, lipid, and phospholipids. Of the 240 proteins in NRL, 60 have been found to be allergenic, causing latex allergy.[5] Natural rubber latex is treated with ammonia and other preservatives after it is harvested, to prevent its deterioration during its mass transport to factories worldwide.[6] Antioxidants and accelerators are later added to further the organic chemical compounding. Finally, mechanical forces, using rollers or rotating blades (mastication), are applied to the rubber.[7]

Vulcanization, the process whereby rubber is heated and chemically combined with sulfur, allows the rubber molecules to cross-link with each other, increasing its elasticity and strength. Accelerators such as thiurams are added to speed the vulcanization process, which takes from a few minutes for small objects to an hour or more for vehicle tires, by speeding the cross-linking of the NRL particles. During the 1830s, many inventors had tried to develop a rubber product that could last throughout the year, because rubber products were not standing up to extreme temperatures, becoming brittle in the winter. Charles Goodyear had been working on this process for many years and while experimenting in 1839, he accidentally dropped India rubber and sulfur on the hot surface of his kitchen stove, inadvertently inventing the process of vulcanizaton.[8] Charles Goodyear patented the process in 1844, earning the title, "Father of the Commercial Rubber Industry."[8]

Natural rubber latex causes various reactions in susceptible individuals. The majority of reactions to NRL can be classified as contact dermatitis: irritant contact dermatitis and ACD; and an immediate hypersensitivity reaction. The immediate hypersensitivity reaction or Type I allergic reaction is an immunoglobulin E–mediated reaction and is the most serious reaction. Signs and symptoms include rhinitis, conjunctivits, generalized urticaria, and mucous membrane swelling. Anaphylaxis is the most dreaded complication.[1]

Irritant contact dermatitis results from prolonged and repeated exposure to an irritant. Prior sensitization is not required and although inflammatory cells play a role in the pathogenesis, it is not mediated by immune lymphocytes. Individuals vary in their response to irritants. An example found in the occupational setting is health care workers exposed to prolonged and repeated exposure to water and detergents in the process of repeated handwashing during patient care activities.

Allergic contact dermatitis is a delayed hypersensitivity reaction (Type IV) mediated by antigen-specific, sensitized T lymphocytes. Following sensitization, a rapid reaction may follow exposure to concentrations of allergen that do not induce inflammation in nonsensitized subjects. Features of ACD are pruritic rash, local erythema, swelling, blistering, weeping, and crusting. Symptoms generally occur 1 to 2 days after exposure, but may also occur several hours to several days after exposure.

Allergic contact dermatitis to NRL gloves is most often mediated by rubber accelerants, namely, thiurams, carbamates, and mercaptobenzothiazoles with thiuram being the most common cause.[1] The main thiurams used industrially are tetramethylthiuram monosulfide, tetramethylthiuram disulfide, tetraethylthiuram disulfide, and dipentamethylenethiuram disulfide. Gloves vary in the amount of extractable thiuram, and certain brands are less allergenic. Contact allergens found in the occupational setting besides latex-related allergens include nickel and chromium in metal workers, rosin used by violinists, and epoxy or formaldehyde resins in spray paints used by painters.[1]

Patch testing, designed for the investigation of delayed hypersensitivity reactions, is used to aid in the diagnosis of thiuram allergy.[1] Small aliquots of suspect chemicals are applied to the uninflamed skin in nonirritating concentrations, typically on the back of the individual. The patches are removed after 48 hours, followed by an initial interpretation of reactions. A final interpretation is made again at day 4 or 5. Reactions are read according to criteria published by the North American Contact Dermatitis Group.[9]

Thiuram should be considered as a reason for delayed hypersensitivity reaction to NRL in health care workers. The

DOI: 10.1097/JOM.0b013e31824be452

identification of thiurams as potentially responsible for an allergic reaction is important, because targeted workplace accommodation can play an important role in the prevention of future allergic reactions once the recognized agent is eliminated. Once the allergen is identified it should be avoided and the occurrence of further dermatitis is then avoided.[1] Natural rubber latex products are being used less frequently in the health care setting because allergy to these products (latex allergy, allergy to thiuram, and other accelerators) has become a more significant problem. Latex safe alternatives are being substituted.[10] However, NRL products are still used in the health care setting as well as in the home. Being cognizant of, and having a high index of suspicion for, the various types of allergic reactions resulting from NRL will assist in prompt and accurate diagnoses allowing appropriate workplace accommodation for health care workers.

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