
Control of occupational asthma and allergy in the detergent industry

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Objective: To provide an overview of how a comprehensive preclinical, clinical, and industrial hygiene program has been successfully used to control allergy and asthma to enzymes used in the detergent industry.

Data Sources: The author performed a PubMed and ToxLine search of English-language articles with the keywords *enzymes*, *occupational allergy*, *occupational asthma*, *detergent*, and *detergent industry* from January 1, 1995, to January 1, 2002. Scientific meeting abstracts, books, and industry association papers on allergy and asthma in the detergent industry were also reviewed. In addition, the practical experience of one major detergent company was included in the review.

Study Selection: All published work on this topic was reviewed, and the work that discussed the key highlights of control of occupational allergy and asthma to enzymes used in the detergent industry was selected for this review.

Results: The detergent industry has developed guidelines for the safety assessment of enzymes, control of exposure to enzymes, and medical surveillance of enzyme-exposed workers. Because of these guidelines, occupational allergy and asthma to enzymes used in the detergent industry have become uncommon events. Cases of disease have been documented in some manufacturing sites that have had poor adherence to the guidelines. Those manufacturing sites that have adhered to the guidelines have had few cases of allergy and asthma to enzymes among exposed workers. A review of medical data from these sites has shown that workers who have developed IgE antibody to enzymes can continue to work with enzymes and remain symptom free.

Conclusions: Occupational allergy and asthma to enzymes used in the detergent industry have been successfully controlled via the use of preclinical, clinical, and industrial hygiene safety programs designed to minimize sensitization to enzymes and development of disease. The basic principles of these programs can be applied to other industries where occupational allergy and asthma to proteins are common.

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INTRODUCTION

The introduction of alkaline and heat stable enzymes into the detergent industry in the late 1960s led to the development of occupational allergy and asthma among workers.^{1,2} It was quickly recognized that these enzymes were potent allergens. In fact, the most significant adverse event associated with enzymes is IgE-mediated hypersensitivity. As a result of this experience, exposure guidelines with stringent exposure control measures were developed for enzymes. This has resulted in a significant reduction in the incidence of occupational allergy and asthma in the detergent industry.³ However, failure to comply with these guidelines has led to recent reports of enzyme-induced occupational asthma and allergy in the detergent industry.⁴ Overreliance on enzyme encapsulation may have been partly responsible for this outbreak.

The Procter & Gamble Company (P&G) has developed a program that uses preclinical data, clinical measurements, and industrial hygiene practices to control exposure to enzymes, monitor the workforce, and intervene before the development of allergic symptoms. This model has the potential to be applied to other work environments where IgE-mediated occupational disease is a hazard. This review was performed to provide an overview of how the P&G program has

been successfully used to control allergy and asthma to enzymes used in the detergent industry. The author performed a PubMed and ToxLine search of English-language articles with the following keywords: *enzymes*, *occupational allergy*, *occupational asthma*, *detergent*, and *detergent industry*. The search was conducted from January 1, 1995, to January 1, 2002. Scientific meeting abstracts, books, and industry association papers on allergy and asthma in the detergent industry were also reviewed. In addition, the practical experience of one major detergent company was included in the review. All published work on this topic was reviewed, and the work that discussed the key highlights of control of occupational allergy and asthma to enzymes used in the detergent industry was selected for this review.

PRECLINICAL PROGRAM

An analytical profile (including immunoanalysis) of an enzyme is needed to characterize the protein content, protein profile, activity, and cross-reactivity to other enzymes. This information is used for the assessment of the allergenic potential of an enzyme, the development of skin prick test (SPT) reagents for the medical surveillance program, and the development of immunoassays used to measure enzyme levels in the air of detergent manufacturing sites.

Animal models have been used to assess the ability of different enzymes to induce an allergic response and subsequently rank the allergenic potential vs a reference enzyme.^{5,6}

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A reference enzyme allergen with an assigned occupational exposure guideline (OEG) is used for comparative purposes; the subtilisin protease Alcalase is used as the reference allergen. Alcalase has an OEG of 15 ng/m³. The guinea pig intratracheal test and the mouse intranasal test have been used to rank different enzymes as more potent to less potent vs the reference enzyme. The potency is based on the antibody response (IgG1 in the guinea pig and IgG1 and IgE in the mouse). The potency difference from the reference is used to assign an exposure guideline for the new enzyme. The OEG is based on protein rather than activity, since the protein content is important for allergenicity; inactive enzyme can be just as allergenic in an animal model as active enzyme.⁷ All enzymes used in detergents have OEGs that range from 2.5 to 15 ng/m³.

The animal models have also been used to show that detergent matrix and active protease enzyme have adjuvant activity and can enhance allergic antibody responses. These observations have been described previously.^{8,9} It is possible that the detergent matrix and/or the protease activity affects the permeability of the mucosal surface, thereby affecting the way immune cells interact with the enzyme proteins. More work is needed to understand this phenomenon. Regardless of the mechanism, the adjuvant activity of the detergent and the protease enzyme must be taken into account when establishing OEGs for new enzymes. We would predict that the sensitization rate to various enzymes would be no different (if not lower) than the rate measured for protease if the OEGs were maintained. Prospective monitoring of the workforce confirms the adequacy of the OEGs for the different enzymes tested in the animal models.^{3,5}

INDUSTRIAL HYGIENE PROGRAM

Adherence to established work practices is key to control of exposure and elimination of allergy and asthma. An industrial hygiene risk assessment is performed to judge how well a manufacturing site can manage a new formula or a new enzyme.¹⁰ The quality of engineering controls, air monitoring, and employee work practices are key elements in the risk assessment process. Engineering controls such as ventilation (room and area), enclosure (specific areas of manufacturing line), spill containment and cleanup (eg, no brooms), and equipment maintenance are important to keep exposures at or below the OEGs. Use of personal protective equipment is reserved for situations that lead to high peak exposures. Personal protective equipment includes gloves, coveralls, and respirators (all employees undergo respirator fit tests and training). Formulating products that produce low dust and aerosol and limiting the amount of enzyme in the formula also contribute to control of exposure. Air monitoring systems, which verify adherence to the OEG, are developed for each enzyme. Therefore, analytical methods to characterize enzyme receipts and measure specific enzymes in the air are in place before the enzyme is introduced into the manufacturing environment. Finally, ongoing employee education and training are key to the success of the program. Employees understand the concepts of type 1 allergy and how

exposure can affect the development of IgE antibody. They are involved in developing work practices that help to minimize contact with enzymes and enzyme-containing products. Ultimately, employees and plant managers are responsible for eliminating or minimizing those work practices that lead to contact with enzymes and enzyme-containing products.

MEDICAL SURVEILLANCE PROGRAM

All exposed employees are enrolled in the medical surveillance program. This is a prospective program that includes a respiratory questionnaire, pulmonary function analysis, and SPT to assess the development of sensitization to each enzyme. The SPT is performed at baseline, 6 months, 1 year, and then yearly after exposure (after introduction of either a new enzyme or a new employee into the manufacturing site). The SPT is used as a "before the fact" measure to identify those employees whose immunological status has changed before they experience an onset of allergic symptoms. When a new SPT positive response is measured, action is taken to reduce or eliminate exposures that may have been associated with the conversion. Workers with a positive SPT result are not removed from the work environment unless they have symptoms that cannot be managed through industrial hygiene control measures. By minimizing contact with enzymes, the industry has been able to minimize sensitization rates and thereby eliminate or greatly minimize the opportunity to have symptoms. It has been P&G's experience that minimizing the rate of sensitization to less than 3% per year will greatly reduce the risk of symptoms. Workers with a positive SPT result can continue to safely work with enzymes and remain symptom free. The concept that the threshold of exposure for eliciting symptoms is greater than the threshold of exposure for inducing IgE antibody was born from these observations.¹¹

CONCLUSION

The enzyme hygiene program has allowed the industry to greatly reduce the risk of inducing occupational allergy and asthma to enzymes in detergent manufacturing sites. When enzymes were first introduced into P&G detergent sites in 1968–1969, 40 to 50% of the plant population became sensitized in a 2-year period. Exposures were estimated to be approximately 30 to 300 ng/m³. Currently, less than 20% of the plant population is sensitized to enzymes during a 10-year period. Exposures are less than 15 ng/m³. There have been no cases of enzyme-induced occupational asthma since 1994 in any P&G detergent manufacturing site around the world. This experience shows that type 1 allergens can be effectively managed to minimize sensitization and eliminate occupational asthma.

Consideration should be given to reapplication of some or all of the elements of the detergent enzyme program to other industries where type 1 allergy to proteins is an issue. The soap and detergent agencies in the United States (Soap and Detergent Association) and Europe (International Association of Soap, Detergent, and Household Product) have prepared

guidelines for the safe handling of enzyme-containing detergents.^{12,13} The reader is encouraged to contact these groups to obtain these publications as a source of information to guide the safe handling of type 1 occupational allergens.

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