*Project S.E.N.S.O.R. News

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ENZYMES AND WORK-RELATED ASTHMA

Enzymes derived from bacteria, fungi or livestock are widely used in commercial products and laboratories. Awareness of their allergenic potential from airborne exposure was recognized in the 1960's when enzymes were first used as additives in cleaning detergents.

Table I lists the enzymes associated with work-related asthma, the source of those enzymes and the industries where the enzymes are used. All the enzymes in Table I have been shown by specific antigen challenge testing to cause asthma. Sensitized individuals have been shown to have both positive skin tests and IgE-specific antibodies to the individual enzymes. The references list the key articles for the medical testing.

The allergic potential of enzymes is not just of importance in the workplace. The etiologic antigens of many common environmental allergens are enzymes. For example, house dust mite antigens include amylase, protease, and trypsin; and cockroach antigen includes a protease.

Determining enzyme-related asthma is no simple task. Specific antigen bronchoprovocation challenge testing is not part of standard medical care. In addition, amylase is the only enzyme for which standard clinical laboratories can measure IgE-specific antibodies. Measurement with skin testing of IgE-specific antibodies to other enzymes or antigens have been developed by individual researchers, but such testing is not available in the normal clinical setting. Further, there are often multiple other non-enzyme-related exposures in the workplace that can cause asthma. Examples of such workplaces include a detergent manufacturer, a bakery, a grain mill, a grain storage facility and a health care setting. Therefore, it is not surprising that it is often difficult to isolate the specific allergen from the clinical history for an individual who develops work-related asthma in these types of industries.

However, the identification of a specific enzyme through a clinical history may be feasible for patients who work in some health care or production settings. For example, if a nurse or pharmacist has an immediate reaction after handling or mixing a pancreatic extract, the clinical history would point to that enzyme as the putative agent associated with the patient's asthma. In a factory setting, a worker with an immediate reaction during the mixing of an enzyme as an additive to a product would point to that enzyme as the agent associated with the patient's asthma. Additionally, peak flow testing or repeated spirometry measurements performed at work and away from work may confirm the work relatedness of symptoms in an industry where enzyme use is the likely asthma-causing agent.

Over the last 25 years, only five work-related asthma patients where the cause was attributed to an enzyme have been reported in Michigan. The following are two examples of the cases reported to the Michigan surveillance system.

CASE #1. *A man in his 50's developed wheezing, cough, chest tightness and shortness of breath eight years after beginning to work at a detergent manufacturer. He was hospitalized twice with the diagnosis of asthma. He had smoked half a pack of cigarettes a day for 30 years. He had a family history but no personal history of allergies. His spirometry showed very severe obstruction (FEV_1 percent predicted of 32%) with hyper-reactivity. The suspected allergens were the protease enzymes Esperase® and Savinase®.*

Table I. Enzymes Used Commercially that are Known to Cause Work-Related Asthma

Name of Enzyme (Brand Name®)	Source	Use
Proteases Amylase Detergents (Termamyl®, Ban®, Duramyl®) Pharmaceutical (Flaviastase®)	*Bacillus subtilis* *Bacillus lichniformis* *Bacillus amyloliguafaciens* *Aspergillus oryzae* *Aspergillus melleus* Cow or pig pancreas	Detergents, Production of sweeteners and alcohol, Bread production, Pharmaceutical production
Bromelain	Pineapples	Meat Tenderizer, Alternative Medication
β-Glucanase	*Aspergillus aculeatus* *Bacillus* *Trichoderma reesi* and *longibrachiatum*	Beer, wine and starch production, Additive to animal feed
Cellulase (Carenzyme®, Endolase®, Celluzyme®)	*Trichoderma viride* *Humicola insolens* *Aspergillus niger*	Detergents, processing coffee, Pharmaceutical production
Lipase (Lipolose®, Lipolase Ultra®, LipoPrime®)	*Aspergillus oryzae* *Thermomcyes lanuginodius* *Candida* *Rhizomucor michar*	Detergents, production of fragrances, baby food, baked goods, pasta and cheese, Additive to animal feed
Lysozyme	Egg whites	Cheese and wine production, Laboratories
Pancreatin Amylase Lipase Protease	Cow or pig pancreas	Pharmaceutical production
Papain	Papaya	Meat tenderizer, Pharmaceutical laboratories, Dentistry
Pectinase (Pectinex®)	*Aspergillus aculeatus* *Penicillum sp.* *Trichoderma sp.*	Production of fruit salad, fruit juice, wine, food coloring, extraction of citrus aroma and production of animal feed
Pepsin	Pig stomach	Food production including cheese, non-dairy snacks, cereals, Leather products, Laboratories
Peptidase	*Serratia*	Pharmaceutical production
Phytase	*Aspergillus niger* Yeast	Additive to animal feed
Pronase (Empynase®)	*Streptomyces griseus*	Pharmaceutical
Protease (Alcalase®, Esperase®, Everlase®, Maxatase®, Neutramase®, Protamax®, Savinase®,)	*Bacillus sp.*	Detergent
Trypsin	Cow or pig pancreas	Plastic production Pharmaceutical production
Xylanase (Pentopan®)	*Aspergillus sp.* *Trichoderma sp.*	Pulp Paper Production, Bakery Clarification of juices Extraction of coffee, plant oils

CASE #2. *A woman in her 50's developed nasal symptoms, wheezing, cough, chest tightness and shortness of breath three years after beginning to work at a pharmaceutical company. She was hospitalized twice for her asthma. She smoked a pack of cigarettes a day for 21 years, quitting seven years prior to the development of her asthma. She had no family or personal history of allergies. Her spirometry showed moderate obstruction. The suspected allergen was a pancreatic extract.*

An interesting observation relevant to Case #1 who had severe obstruction is that exposure to high airborne concentrations of proteases in animal experiments have caused emphysematous lesions. These experiments were initiated given the known destructive effects of proteases on tissue. Further, there is limited evidence of increased prevalence of emphysema in a study of papaya-exposed and detergent-exposed workers. Additionally, proteases may cause a non IgE-based inflammatory reaction. Trypsin, in addition to having proteolytic activities, act as cell-signaling molecules in the airways where there are protease-activated receptors. Trypsin added to *in vitro* guinea pig bronchi invoked contractions.

There are at least 100 genetically engineered enzymes that are commercially available. There are no specific OSHA standards for enzymes, which are regulated as nuisance dusts. Permissible exposure limits for nuisance dusts allow exposures to be high enough to see dust in the air. Encapsulation of the enzymes in the detergent industry has reduced exposure and the incidence of sensitization among workers in that industry, but has not eliminated sensitization completely. Health practitioners should have a high level of suspicion for any patient with asthma who works with any enzyme, even those not listed in Table 1, as potentially capable of causing sensitization and asthma.

As always we are interested in receiving any reports of known or suspected work-related asthma from enzymes or other workplace agents. Please call Kenneth Rosenman, M.D. at 1-800-446-7805, if you have any questions or if we can be of assistance in diagnosis or management.

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*PS *Remember to report all cases of occupational disease!*

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