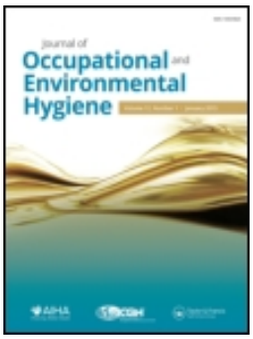

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Managing the Risk of Occupational Allergy in the Enzyme Detergent Industry

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Enzyme proteins have potential to cause occupational allergy/asthma. Consequently, as users of enzymes in formulated products, detergents manufacturers have implemented a number of control measures to ensure that the hazard does not translate into health effects in the workforce. To that end, trade associations have developed best practice guidelines which emphasize occupational hygiene and medical monitoring as part of an effective risk management strategy. The need for businesses to recognize the utility of this guidance is reinforced by reports where factories which have failed to follow good industrial hygiene practices have given rise to incidences of occupational allergy. In this article, an overview is provided of how the industry guidelines are actually implemented in practice and what experience is to be derived therefrom. Both medical surveillance and air monitoring practices associated with the implementation of industry guidelines at approximately 100 manufacturing facilities are examined. The data show that by using the approaches described for the limitation of exposure, for the provision of good occupational hygiene and for the active monitoring of health, the respiratory allergenic risk associated with enzyme proteins can be successfully managed. This therefore represents an approach that could be recommended to other industries contemplating working with enzymes.

Keywords consumer products, detergents, enzymes, IgE allergy, industrial hygiene, occupational allergy, occupational hygiene, risk assessment

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INTRODUCTION

It has been known for several decades that enzymes, such as those of bacterial, plant, and fungal origin, have the potential to cause occupational respiratory allergy, even asthma, depending on exposure levels and conditions.[1–6] As a direct consequence, it is necessary to control occupational exposure to enzymes so that the risk is appropriately controlled. Additionally, it is necessary to monitor the working environment and the workforce to ensure that exposure control is being adhered to, and that impacts on employee health are minimized. In the United States and Europe this has led trade associations to issue best practice guidelines, based on the accumulated experience of the detergent industry, which detail how to handle enzymes safely in the factory situation.[7,8] Key elements of these guidelines are presented in Table I.

Independent commentaries in this area have also appeared. For example, the American Conference of Governmental and Industrial Hygienists (ACGIH®) has addressed the general topic of the safety of enzymes, with particular focus on the endpoint of respiratory sensitization.[9] The United Kingdom (UK) and The Netherlands also have addressed the issue.[10,11]

Evidence has been presented showing that adherence to best practices can deliver a safe working environment.[e.g. 5,12–15] There is also good evidence that failure to implement adequate operating standards can result in occupational health problems.[16–19] Although the precise boundary between what

TABLE I. Key Elements of Best Practices Guidelines for Use of Detergent Enzymes[7,8]

	Exposure Control Element	Description
Plan	Enzyme raw material quality and form (granulate and tablet detergent operations)	Encapsulated enzymes, not powders, are used for production of granulate or tablet forms of detergent products to reduce dust generation. *Note: Liquid enzymes are not encapsulated representing a different exposure scenario in which added care must be taken to control exposure.*
Plan	Equipment handling enzymes or enzyme- containing products q43 designed to follow the hierarchy of controls with the first principle to incorporate exposure prevention into the design of equipment and processes.	1. Equipment handling enzymes or enzyme-containing products are designed to reduce exposure through use of local exhaust ventilation and intrinsic spill prevention systems and all processing equipment is designed to be leak-free, reliable, and minimize damage to raw materials and packaging. 2. General ventilation in the workplace is installed as needed to reduce the likelihood and duration of exposure during, cleaning, inspection, and maintenance activities.
Plan	Safe practices, cleaning methods, and administrative controls are developed to ensure that exposures during both routine and non-routine product tasks are in place.	Qualitative and quantitative exposure assessments are part of the system for managing change to ensure that safe practices, methods of cleaning, and proper use of protective clothing and respiratory protection are developed and clearly identified to potentially exposed employees.
Do	All employees are provided with training on possible sources of exposure, the appropriate countermeasures to prevent exposure, and the required maintenance of all equipment handling enzymes.	1. Safe practices for prevention of exposure are understood by employees as are the countermeasures needed to prevent exposure. 2. Employees are clear about the importance of conducting preventive maintenance on enzyme manufacturing equipment as well as local exhaust and general ventilation systems. A preventive maintenance program exists for all equipment which identifies a responsible party.
Check	Performance assessments are routinely conducted on the status of equipment and of safe behaviors in the workplace. All levels of the operation participate in these programs to reinforce the key elements of exposure prevention.	Compliance targets are established which at a minimum cover: 1. Quantitative and qualitative exposure assessments for detecting sources of routine and peak exposure. 2. Equipment condition assessments 3. Behavior observation or other behavior-based safety techniques are used to reinforce safety practices, proper cleaning and maintenance of equipment, and proper use of protective clothing and respiratory protection. 4. Medical surveillance including a respiratory questionnaire and skin prick testing or serological testing is recommended.
Act	Investigations for all items that do not meet established compliance targets are completed and corrective actions and follow-up are completed to deliver improved performance against those success criteria.	

is best practice and what is inadequate is rarely well defined, as this will vary across different industrial situations, ingredients, and specific detergent formulations. It has therefore been proposed that a maximum exposure limit (DMEL) of 60ng/m^3 for pure enzyme protein provides an appropriate starting point for setting specific occupational airborne exposure limits for the detergent industry [20] and that industry guidelines provide the necessary information on which to base exposure control, and air and health monitoring strategies.[7,8] This is fully consistent with the requirements of regulations such as those in Europe—**R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals (REACH) [21] Thus, the understanding of how stringent the occupational exposure limits (OELs) need to be, how effective the occupational hygiene needs to be, and how important it is to back this up with regular airborne monitoring in the workplace and health monitoring of the workforce is critical to success.

This experience is based also on the distinction between the detectable induction of enzyme specific IgE in an individual compared to the expression of the clinical symptoms of allergic disease, which are related but separate events that must be managed when working with occupational allergens. In the detergent industry, measurement of the specific allergic immunoglobulin E (IgE) antibody response and management against this response provides a clear point of control in the successful (and long-term) prevention of occupational allergic respiratory disease to enzymes.

In addition to health surveillance and air monitoring, workforce education in occupational hygiene practices and the proper use of respiratory protective equipment for higher risk activities and abnormal events forms an essential part of the safe working environment. In this article, the practical implementation of the industry guidelines is examined, with a focus placed on air monitoring strategies and approaches to health surveillance. Information has been obtained from a number of companies involved in the use of these ingredients in the production of enzyme-containing detergents. This knowledge is critically reviewed in relation to the American (ACI) and European (AISE) guidelines (Table I)[7,8] and particularly in terms of how the air monitoring and health surveillance information generated can be used as a feedback loop which allows for the identification of problem areas and/or use in continuous improvement.

HEALTH SURVEILLANCE

This review commences with health surveillance, not least since this is the first activity that should occur with any new employee (full-time or part-time) before starting to work with enzymes and who may therefore be exposed to airborne enzyme during the course of their employment. Of course, it is paramount that a new worker should then be able to enter a working environment which is known to be safe, a matter which is dealt with in a subsequent section of this article. Similar considerations may also be applied to contractors, but such a decision has to be taken on a case-by-case basis.

The overall aims and strategies for ensuring proper health monitoring are contained in industry guidelines[7,8] and details of their implementation have been described for one company. [15] For each company involved in the preparation of this present publication, all new employees participate in a pre-placement health screening, which results in a detailed health evaluation at the start of their employment. Although some specific details may vary, this includes a health questionnaire, including a focus on any history of respiratory allergies, a lung function test, and a test for specific allergies either by a skin prick test or evaluation of serum IgE. Then in the first 1 to 2 years of employment, this process is repeated at 6-month intervals. Subsequently, the surveillance is carried out annually.

The initial health screen is very important. Not only does it provide some insight into individual potential to experience effects based on the medical history, it provides an individual baseline on lung function (e.g., FEV_1, the forced expiratory volume delivered in one second; PEFR, peak expiratory flow rate; FVC, forced vital capacity) together with baseline data on the presence of IgE which may cross react with the enzymes to which the new worker may be exposed. The presence of such (potentially cross-reactive) antibodies has long been recognized.[22,23] Of course, the process also records whether an individual has any previous occupational exposure to enzyme allergens. It is assumed that all individuals may also have had consumer-level exposure to enzyme allergens, but the evidence is that this exposure does not induce sensitization of the respiratory tract.[7,20] Consistent with this, is the initial screening for enzyme specific IgE, where a positive result is extremely rare.

The most obvious difference in approach between the companies is that some companies elect to identify the presence of enzyme-specific IgE via skin prick testing, whereas as others undertake serological analysis. Each approach has some advantages and disadvantages, but it is generally held that the methods provide broadly equivalent results when interpreted appropriately (e.g.,[24]). The pros and cons of these different approaches are fully detailed elsewhere. [8] Obviously, once a particular approach has been adopted, then it should be maintained to provide a consistency of monitoring at a location to allow comparisons over time. Minor differences exist also in other surveillance aspects such as the fine detail of the medical questionnaire and in the frequency of its application, particularly for new workers. However, all participating companies meet both the spirit and the letter of the industry guidance[7,8]

In some cases, the frequency of health monitoring may be increased, for example if a new enzyme is introduced into the factory. It may also be changed if there is evidence of a problem which suggests an increased frequency would be appropriate, either for an individual or a specific workforce group or in relation to a particular task/activity.

In relation to the risk of the development of IgE-mediated allergy to enzymes, it is the induction of specific IgE which forms the central component of health surveillance. The presence of induced IgE is not, of itself, an adverse health effect,

TABLE II. Overview of Health Surveillance Experience in the Detergent Industry

Year	No. of factories	No. of workers	Uptake [A] (%)	Incidence [B] (%)	Prevalence [C] (%)	Symptoms [D] (%)
2006	107	22100	96.0	0.99	8.6	0.11
2007	109	23668	95.6	0.76	8.1	0.08
2008	114	23976	94.4	1.04	7.8	0.26
2009	106	22686	97.0	0.82	7.3	0.05
2010	106	24773	94.9	0.97	8.5	0.05

[A] The percentage of the workforce that participate in the surveillance programs.
[B] The percentage of new cases of sensitization during the calendar year.
[C] The prevalence of sensitization in the exposed workforce.
[D] Evidence of rhinitis, conjunctivitis, impaired lung function, asthma not clearly linked to a non-occupational causation.

but should be regarded as a marker of exposure and thus a risk factor for potential respiratory allergic disease. Additionally, its principal value is to provide a quantitative control point which can be considered in relation to the information derived from regular air monitoring and other behavioral safety-based audits. For technical analytical considerations, the majority of air monitoring data is generated via high volume area sampling and that the data is not indicative of any individual's personal exposure per se.

Table II provides an overview from the participating companies covering the period 2006–2010 inclusive. Information for more than 20,000 individual workers from over a hundred globally distributed factories (every continent, excluding Antarctica) is summarized. The data supplied was anonymized by the companies involved. The practical experience is that new cases of sensitization (yearly incidence rate) in these facilities typically are below 1%, with clinical symptoms occurring in less than 1 in 10 of these sensitized individuals, i.e., in less than 0.1% of the overall exposed population.

The clinical symptoms include evidence of rhinitis, conjunctivitis, impaired lung function, or asthma, not clearly linked to a non-occupational causation, always remembering that a decision between occupational and non-occupational depends on the opinion of the occupational physician reporting from each plant. Even without reporting bias, this distinction is often difficult even for occupational asthma/rhinitis experts. The physician's diagnosis of asthma, based solely on clinical symptoms, can sometimes be tenuous; sensitization plus the development of symptoms matching the pattern of exposure is not 100% reliable, but in the absence of other evidence must be taken as conclusive. Although specific inhalation challenge (also known as bronchial provocation testing) can help clarify an enzyme's role in eliciting symptoms, in practice it is rarely needed to make a diagnosis of enzyme asthma. This procedure must be done only in experienced clinical laboratories with a track record for quality and safety. [25] Relevant clinical symptoms in workers without a positive IgE test are essentially unknown.

Importantly, worker participation (uptake) in the health surveillance programs across these factories on average exceeds 95%, this being despite the fact that in a number of locations, such participation must be entirely optional to comply with local regulations (and a 100% participation figure is almost impossible due to starters, leavers, and long-term absence for a variety of reasons, including maternity leave). Analysis of the data by geographical region is not possible, but anecdotally there is little difference, but this has to be considered in relation to use levels of enzymes, which also vary regionally, as well as between companies.

When considering the incidence of new sensitizations, there is a published view that, as a general principle, an annual incidence of 3% or less should be the target for new IgE-positive workers in the complete absence of clinical symptoms. [12] Clearly, on the data presented herein, this target is typically bettered, and by a substantial margin—see Table II. In fact, for every participating company and for each year of this review, the 3% target was bettered, excepting a single occasion when it was equaled. Within a company, occasionally, a particular factory location may exceed the target by a small margin. This already provides an alert signal for future intervention. However, whatever the action standard, it remains the case that it is the induction of a low level of enzyme-specific IgE that provides the earliest marker of potential future respiratory allergy. Where IgE induction occurs at an elevated frequency, it represents a trigger for action. Such actions could include workplace investigations, an increased or refined air monitoring strategy and a review of occupational hygiene requirements.

The monitoring described previously ensures that risk management measures and exposure controls remain effective, thereby protecting individual worker's health; where issues arise, it also facilitates focused intervention to resolve the problems identified.

Besides IgE testing, it is also important to identify symptomatic individuals through periodic health screenings, including respiratory questionnaires and lung function tests. Additionally, all enzyme exposed individuals should be educated in the symptoms of upper respiratory allergy (rhinitis and conjunctivitis) and lower respiratory allergy (asthma) and should be advised to expeditiously report the occurrence of

these symptoms to their occupational health provider. An investigation should then be conducted to determine if these symptoms are work-related.

The development of work-related allergic rhinitis does not necessarily imply that the affected individual must immediately be restricted from further work with enzymes. Oftentimes, reinforcement of work procedures and proper respirator use during peak enzyme exposure situations may be all that is needed to prevent further symptoms. These individuals may require more frequent health screenings to monitor them for changes in health status. An individualized return to work plan should be developed. For example, employees with *suspected* occupational enzyme asthma require pre- and post-shift lung function tests, or peak expiratory flow measurements, to ensure that their protection from exposure is adequate and that they are not developing chronic low-level lung inflammation. In reality, the development of persistent work-related symptoms is an indicator that reassignment away from enzyme exposure will be the most appropriate course of action, in line with the recommendations of several expert bodies such as the American College of Chest Physicians and the European Respiratory Society.[26,27] In the rare situation where occupational asthma has developed, the experience is that removal from exposure is necessary.

AIR MONITORING

This activity is the essential complement to health monitoring (which makes it unfortunate that we have not been able to collate data from as many factories, but this arises solely from a pragmatic decision concerning the law of diminishing returns—factories have not always archived results over a period of years in a manner designed to facilitate retrospective analysis for the purposes of this review!). The aim of air monitoring is to confirm that the occupational hygiene measures put in place are functioning in such a way as to ensure that the defined occupational exposure limits (OELs), set either by national regulation or by individual companies, are met and are maintained, so that any trends to the contrary can be dealt with before the OEL is exceeded. OELs for airborne enzymes are based on the recommendations proposed many years ago [26] and more recently reconfirmed.[9,20] From this work arises the defined maximum exposure level (DMEL) of 60ng/m^3 for enzymes, which provides a suitable starting point for the definition of specific enzyme OELs. For example, in the presence of substances which may enhance the allergenicity of enzymes, such as surfactants, lower OEL values may be adopted internally by individual companies. [12] For the detergent manufacturing industry, typical OELs for enzymes are 6 to 15 ng/m^3.

Air monitoring for enzymes is complicated by the relatively low OEL values. As a consequence, high volume air samplers deployed for several hours are a common feature in the approach adopted by the majority of the industry participants. Typically, flow rates are in the region of 600 L per min for powders and approximately half that rate for liquids, e.g., with sampling times between 1 to 4 hours in both cases. The lower flow rate may be necessary for liquids to avoid airborne aerosols being pulled through the filter and thus lost from the sample. Lower-volume samplers may also be used, but the overriding factor is that the monitoring process has to be sufficient, in combination with the subsequent analytical method, to have an appropriate power of detection. This type of monitoring is generally applied to selected target areas in a factory, with the number of samplers depending on the size of the factory and the complexity of the process (but often therefore this means at least 10 samplers per site). The target areas are chosen on the basis of perceived risk, backed up by experience. For routine monitoring, samplers are typically used every day in each location, with some locations even being checked more than once per day, e.g., every shift during 24-hour working. Experience may also show that sampling frequencies lower than daily, perhaps even only weekly may be sufficient when the standard of process containment and control is superior.

Where enzyme use is intermittent, air monitoring is applied in a more focused fashion, dependent again on the assessed risk. However, in any situation, to ensure that feedback from the sampling strategy is of greatest value, enzyme analyses and reporting is generally rapid, within a few hours of the sample being taken. This will provide the opportunity to intervene should any sample indicate a potential deterioration in control measures, or return a result that exceeds a defined OEL.

TABLE III. Overview of Air Monitoring Experience in the Detergent Industry

Year	No. of factories	No. of readings	No. above action standard	Incidence [A] (%)
2006	82	288318	1592	0.55
2007	83	276193	1344	0.49
2008	89	267147	2546	0.95
2009	90	306986	2400	0.78
2010	95	344853	1715	0.50
Mean	**88**	**296681**	**1919**	**0.65**

[A] Proportion of readings above the action standard (i.e., 60ng/m^3 or lower; typical occupational action standards for enzymes are 6 – 15 ng/m^3).

Table III displays an overview of air monitoring data from approaching 100 detergent factories. It shows that up to approximately 10 measurements per day are made, with less than 2 per month showing an airborne level above datum (typical occupational exposure guidance/occupational exposure limit values for enzymes are 6 to 15 ng/m^3). The actual figures were not retrieved, but it is common experience that values above datum are, in the very large majority of cases, minor digressions. In reality, the majority of values are close to the limit of detection. A more serious increase above datum, for example double the level, is an extremely rare event, one which would signal the need for rapid corrective action.

Currently, air monitoring in effect offers only a measure of the average exposure over the time period during which the air was sampled. The positioning of samplers has to be such that they are most appropriate, i.e., at the highest risk areas.[8–10,28] It can be argued that peak exposures may be of greater importance than prolonged lower-level exposure, but a detailed immunological debate is outside the scope of this article. Currently, the analytical power necessary to routinely perform continuous monitoring at the ng/m^3 level required does not exist. Proper occupational hygiene, including control of airborne exposures, should ensure that exposure levels are below datum, so that order of magnitude or greater peak exposures do not occur, except in the case of industrial accidents.

CONCLUSION

Exposure to enzymes presents a potential risk to human health.[1–4] In the occupational setting, this risk can readily be expressed if the exposure is not tightly controlled.[5–9] Consequently, monitoring of airborne exposure against stringent OELs coupled with regular surveillance of the health of the potentially exposed workforce is required to deliver assurance of a safe working environment. That an individual company can achieve this has been previously reported independently [15]; that it can be more broadly achieved by both enzyme producing and enzyme using companies forms the substance of this present review. In the 5 years of experience reviewed herein, results from air monitoring and health surveillance show that the companies involved have been able to meet the standards set by the broadly accepted industry guidelines.[7,9]

The results from this 5-year review of air monitoring and health surveillance in detergent factories using bacterial and fungal enzymes confirm that the approaches described for the limitation of exposure, for good occupational hygiene, and for active health monitoring, mean that the respiratory allergenic risk associated with these proteins can be managed to ensure the safety of the workforce. The results therefore reinforce the view that the current occupational hygiene controls and health monitoring strategies developed by ACI and AISE represent an approach that might be adopted by other industries contemplating working with enzymes.

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