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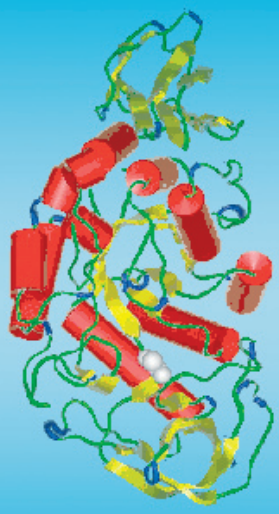
Association Internationale de la Savonnerie, de la Détergence et des Produits d'Entretien
International Association for Soaps, Detergents and Maintenance Products



DEVELOPING CONSUMER PRODUCTS CONTAINING ENZYMES:

ENSURING CONSUMER SAFETY

Working together for a cleaner Europe

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TABLE OF CONTENTS

DEVELOPING CONSUMER PRODUCTS CONTAINING ENZYMES: ENSURING CONSUMER SAFETY

Disclaimer

This document is written for use by the cleaning products industry. However, the practices set forth in this document may also be used as a reference by other industries. This document is based on information gathered at the time of publication (April 2006). Anyone using this publication should check reference sources to make sure that information provided in this document is still correct.

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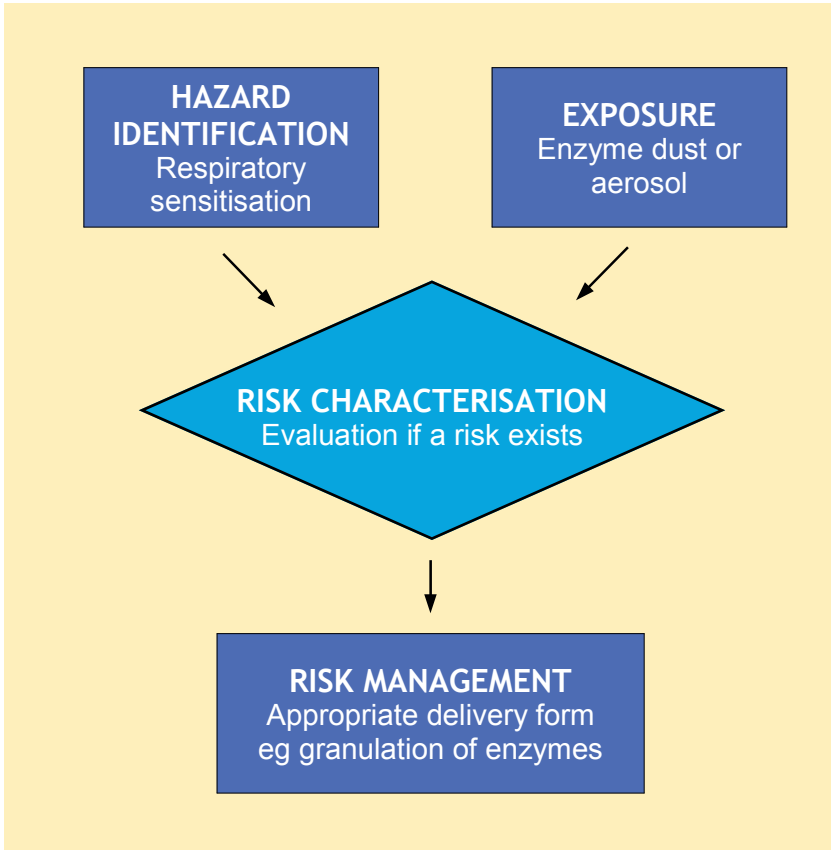
PURPOSE

What are enzymes?

Enzymes are proteins produced by all living organisms. They act as catalysts to increase the rate of chemical reactions. Enzymes used in consumer products usually "break down" certain organic materials into their basic components. For instance, protease in laundry detergents breaks peptide bonds in the proteins that make up food stains. Other ingredients in the detergent are able to remove the broken-down products formed from the action of enzymes more easily than if the enzymes were not in the product. The remarkable property of enzymes is that they complete reactions without being destroyed, allowing a single enzyme molecule to catalyse many individual reactions. They can therefore be used at relatively low levels in consumer products and still ontribute significantly to product performance.

The purpose of this guidance is to describe the key health hazards of enzymes and provide a framework for manufacturers to assess consumer safety of detergent products into which enzymes have been incorporated. Manufacturers of other enzyme-containing products may also find this document useful. The guidance represents a digest of the main points of the United States Soap and Detergent Association document 'Risk Assessment Guidance for Enzyme-Containing Products' (SDA 2005) and captures relevant key points from the Human and Environmental Risk Assessment project (HERA 2005) on the use of proteases in laundry and cleaning products. This document provides technical guidance so that risk assessments can be carried out in a consistent manner across the detergents industry and in a way that is as closely aligned as possible to existing EU risk assessment developments.

THE FOCUS OF ENZYME RISK ASSESSMENT



BACKGROUND

Enzymes have a very good safety profile but, as with many other proteins, they can act as respiratory sensitisers and so may lead to allergy symptoms, such as asthma. This potential risk is the focus for safety assessments for enzymes, and must be managed carefully. The current use of enzymes in consumer products does not pose a risk of skin or eye irritation and so is not discussed further here. Experience in the cleaning products industry demonstrates that the potential risk of adverse effects can be successfully managed by the strategies outlined in this document.

Are enzymes safe for consumers?

Yes, the present use of enzymes, such as in laundry and cleaning products, is safe for consumers. However, enzyme dust or aerosols may potentially lead to the induction of allergen-specific immunoglobulin E (IgE) antibodies, and upon further exposure may elicit respiratory allergies amongst workers employed in the manufacture of such products. Since the early 1970s, detergent enzymes have been incorporated as practically non-dusty, granulated and coated enzyme preparations or used in liquid formulations. In combination with the implementation of improved handling procedures and manufacturing controls, the incidence of respiratory allergy symptoms has been virtually eliminated in the workplace. Several studies have demonstrated that the risk of consumers being sensitised is negligible and provide compelling evidence that enzymes can be used safely in consumer products. This evidence is supported by widespread consumer experience over several decades.

RISK ASSESSMENT PROCESS

What is a risk assessment?

Risk assessment is the process of identifying the hazard profile of a material and gauging the likelihood of adverse effects occurring during handling or use. The objectives of the risk management process are to determine the significance of risks to human health, to ensure that the exposure from product use is and remains within the acceptable risk levels, and to communicate risks, or lack thereof, to appropriate audiences and in an effective way.

Risk assessment provides useful information in order to weigh-up and analyse alternatives, as well as a means of organizing information, so that an estimate can be made of the potential impact on human health. In doing so, assessments may convey a level of precision that fails to reflect the shortfalls of the underlying assumptions and the uncertainties that may characterise the risk assessment.

The quality and reliability of the risk assessment is dependent on, and is only as good as, the data used to conduct the assessment.

Uncertainties may exist in dose-response relationships, exposure data and estimates from exposure models. Assumptions and estimations need to be stated clearly as they can affect the reliability and quality of the risk assessment. It is important to consider these points when evaluating information from the risk assessment and in determining whether or not the risk is considered acceptable.

Risk assessment can be divided into four areas:

- hazard identification;
- dose-response or benchmark identification;
- exposure assessment;
- risk characterisation.

The risk assessment process for enzymes follows this general approach. Benchmark doses to define effect and no-effect thresholds are used instead of classic dose-response curves.

The figure on page 5 outlines the risk assessment process used for enzyme-containing products. A risk assessment guidance document can be downloaded from the HERA website - www.heraproject.com.

Hazard identification

Hazard identification is the characterisation of the fundamental physical, chemical and biological effects of a material. The toxicology of enzymes is unremarkable. Acute and sub-chronic toxicity is not of concern for (industrial) enzymes. The most significant hazard identified is allergy due to exposure via inhalation.

Dose-response or benchmark identification

In this step of the risk assessment process, the relationship between the level of exposure and the specific biological effect is characterized. Since the dose-response relationship for enzyme allergy is not fully characterised and there are gaps in our understanding of the relationship between exposure, sensitisation and symptoms, benchmarks are generally used to support decisions in enzyme risk assessments.

Such benchmarks are based on studies in which measured or estimated exposure levels are associated with a demonstrated specific biological effect (such as whether an allergen-specific antibody is produced) in those exposed. A clear benefit of this strategy is that it can be based entirely on human data. More detailed information can be found in the HERA risk assessment on the use of proteases in laundry and cleaning products (HERA 2005).

Exposure Assessment

Exposure assessment establishes the amount of enzyme to which the user may be exposed during intended use, foreseeable misuse and accidents. This value is then compared to the benchmark exposure in order to make risk decisions. Measuring, or even estimating, exposure to enzymes is not necessarily a simple process. However, the determination of consumer exposure values is needed for carrying out these risk assessments. In the absence of good quality exposure data, conservative worst-case assumptions and uncertainty factors are employed, which lead to an overestimation of exposure levels and thereby limit unnecessarily the amount and type of enzyme that can be used in a consumer product. It is therefore important that the exposure assessment be conducted thoroughly, in order to enable the optimum use of enzymes in consumer products. The most important step of an exposure assessment is trying to define the factors that may influence the exposure.

Risk Characterisation

Risk characterisation is the examination of the relationship between human exposure (calculated or measured) and the inherent toxicity of a substance, in order that the likely incidence and severity of any effect can be assessed. This step is important because it integrates information regarding the hazard identification and exposure assessment associated with use and foreseeable misuse of a product. It should be recognized that risk assessment is a continuously evolving discipline. In the future, the methods and procedures used by practitioners should be modified, as necessary, to reflect the most current scientific practices.

The quality and reliability of a risk assessment is dependent on and is only as good as the data used to conduct the assessment. Uncertainties may exist in dose-response relationships, exposure data and estimates from exposure models. Assumptions and estimations need to be stated clearly as they can affect the reliability and quality of the risk assessment. It is important to consider these points when evaluating information from the risk assessment in determining whether or not the risk is considered acceptable.

What is an exposure assessment?

Exposure assessment establishes the amount of an enzyme to which the user may be exposed during intended use, foreseeable misuse and accidents. The determination of consumer exposure is needed for carrying out a risk assessment.

For a detailed description of how exposure is assessed, see the Annex.

RISK MANAGEMENT PROCESS

The objectives of the risk management process are to determine the significance of risks to human health, to ensure that the product use is and remains within the acceptable risk levels, and to communicate risks, or lack thereof, to appropriate audiences, and in an effective manner.

Risk Control

In general terms, the risk control step of the risk management process should strive to reduce the risk by limiting exposure to enzymes in the product. Risk reduction options may include product modification, product use restrictions or a decision not to market the enzyme-containing product. Modification options may include changing the matrix or delivery system of the enzyme product, reducing the enzyme concentration in the product, substituting other ingredients that may be affecting the potency of the enzyme, or a combination of these approaches. In the detergent industry, great steps have been taken to minimise risk through product modification. For example, enzymes are now encapsulated in order to limit consumer and worker exposure. This risk control method was relatively easy to achieve for consumer laundry products and, in turn, provided a reduction of risk in the work environment and to the consumer.

Risk Communication

An integral part of the risk management process is to communicate enzyme product benefits, as well as potential risks, to appropriate audiences in an effective way.

There are two important audiences to target in designing a risk communication program:

- users of the company's products;
- other stakeholders, such as the general public, governmental and non-governmental organizations, or industry partners.

Product labels are the primary means of communication with consumers. For enzyme-containing products, as with all consumer products, product labels are a mechanism for communicating composition of the product, first aid information, appropriate warning statements, and use and handling guidelines with detailed examples of correct use and concrete recommendations to steer consumers from misuses. An important route toward gaining the acceptance of stakeholders is through interaction amongst experts, either in the field or in industry or government authorities, and amongst interested stakeholders, such as consumer associations, scientific journalists and academia. By providing information to the appropriate audiences, it is possible to promote the safe use of the product and, in turn, reduce the risks associated with exposure to the enzymes contained in the product.

CONCLUSIONS

Enzymes can bring significant benefits to detergent products, including improved efficiencies and previously unavailable product benefits. However, prior to introducing an enzyme preparation into a product, a risk assessment must be conducted to ensure the safe use by the consumer. The primary challenge associated with enzyme use is preventing the generation of allergen-specific antibodies and the development of symptoms of Type 1 hypersensitivity in consumers.

Experience in the cleaning products industry demonstrates that potential risk of adverse effects can be successfully managed by identifying the hazards to be addressed, carefully assessing exposure, characterising the risk and then applying appropriate risk management. This document has outlined strategies and methods that have been used successfully by the industry.

What should companies do?

Each company that intends to use enzymes in its products has to play its role in understanding and managing the risks associated with enzymes. If the risk is not appropriately managed, the consequences for consumer health may be very significant and may spread beyond a single product or company.

It is therefore essential that companies using enzymes in products consider very carefully how they are ensuring consumer safety.

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ANNEX

How exposure is assessed: the details

A. Factors influencing exposure

How might the product user be exposed?

The most common routes of exposure are:

Inhalation The major route of exposure to be considered is inhalation of dusts or aerosolised products. This may arise from intentional or accidental pouring of powdered or liquid products, stirring or agitating product solutions (such as through hand laundering), spray applications, or blowing or vacuuming powder products or liquid products that have dried (for example in carpet cleaning).

Eyes Exposure to enzymes in the eyes is possible by accidental exposure (for example through splashing or hand-to-eye contact) or by misuse (such as in the cleaning of contact lenses).

Skin Skin exposure during product use may be intentional (for example through the use of handwash laundry and cleaning products), unintentional/accidental (such as during pouring of machine laundry detergents) or during misuse (for example through use as a personal washing product).

Product formulation and delivery mechanisms

For liquid products, the formation of aerosols can be affected by delivery mechanism and viscosity of the product. Aerosols should be characterized in terms of their droplet or particle size distribution. The size of droplets or particles, along with their density, determines their rate of settling and, thus, the concentration of enzymes in the air during and after use. Large droplets or particles have the advantage of settling out of the air quickly. The enzyme form can affect the potential for dust generation. Detergents enzymes are encapsulated in order to greatly reduce the potential for dust generation. For these reasons, commercial enzyme granulate preparations do not result in any significant level of inhalable particles during normal handling (SDA, 1995). However, encapsulated enzymes, whilst an important and effective means of reducing dusts generated from enzymes, can break down during manufacturing processes by mechanical action. Hence, encapsulation does not represent a complete solution to preventing exposure to enzyme dusts.

For products that dry after application, the degree of enzyme released as dust should be assessed. Deposition of enzyme residue on hard surfaces, skin and clothing can result in the enzyme becoming airborne and therefore resulting in secondary exposure (see HERA 2005, SDA 2005).

Regional differences in product formulation may also influence the amount of enzyme released as dust and aerosols. For example, laundry detergents are more concentrated in Europe than in the United States to accommodate differences in water temperatures and the design of washing machines.

Overall risk assessment can be optimal if comprehensive answers to these four questions are obtained:

- ***How is the user exposed to the product?***
- ***What is the formulation and delivery mechanism of the product being assessed?***
- ***How is the product going to be used under normal conditions and what might be conditions of foreseeable misuse (including frequency and duration) or accidental exposure?***
- ***Where will the product be used?***

Measurement process

1 Exposure simulation

The exposure simulation procedure used should be based on habits and practices data, including visual observation of product use habits.

2 Sample Collection

Sample collection can vary depending on the type of exposure being assessed. Validation of the procedure and equipment should be conducted prior to making the exposure assessment. Validation is necessary to ensure that new data can be compared to values obtained previously.

3 Measurement of enzyme concentration in samples

There are two main approaches that can be used for measurement of enzyme concentrations in air samples (A.I.S.E. 2002). A longstanding approach has been the use of activity measurement to detect the enzyme and then converting the value to enzyme protein based on specific activity. A more specialised direct measurement of the enzyme in the product is through use of immunological methods, such as the Enzyme Linked ImmunoSorbant Assay (ELISA).

4 Background assessment and carryover prevention

Before conducting any exposure measurements, an assessment of the test area for the presence of contaminating enzyme should be performed. Moreover, the tester should demonstrate the ability to remove any enzyme left from one exposure simulation trial before conducting the next trial.

When formulating a product, consideration should be given to how the design of the delivery system can affect user exposure. Packaging can have a big impact on the extent and route of exposure to the product. A spray delivery system has the highest potential for inhalation exposure and should be designed carefully to minimize the production of inhalable mists. The delivery system should minimise enzyme availability by limiting the production of particles small enough to be captured in the inhaled air stream. An individual assessment of each type must be made, as nozzle design, product viscosity, foam strength and particle size distribution are important in relation to the formation of inhalable aerosols.

An additional consideration should be the effect of 'bounce back' (the product bouncing off a surface that is being sprayed), which may generate smaller droplets or particles than those originally produced by the sprayer. Therefore, an assessment of exposure should not only include the product as it is delivered from the bottle, but should also include an evaluation of secondary exposures such as aerosols generated during bounce back.

How is the product going to be used under normal conditions and what may be the conditions of foreseeable misuse or accidental exposure?

For product use under normal conditions, the amount of product used per application, the duration of usage and the frequency of use are factors that affect the exposure to the product. Knowledge of the habits and practices of product users is important for a thorough understanding of enzyme exposure during the usage of a product. These data can be obtained by consumer tests, surveys and questionnaires, and through poison control centres, government agencies such as inspectorates, manufacturer's help-lines and publications.

To illustrate worst-case scenarios, consider possible cases of laundry detergent misuses, such as hand washing, bathing, hair washing, pet washing, carpet and furniture cleaning, car washing, hard surface cleaning or using the product in a pump spray bottle. Non-recommended uses of a product may be more common in some parts of the world than others and in certain socio-economic segments of the population. These differences should be investigated carefully to ensure proper characterisation of exposures in all markets across the world.

Where will the product be used?
Factors such as room size and ventilation will affect exposure. Use of a product outdoors, where there are air currents, can lead to a different exposure in the breathing zone of the user, compared with use of a product in a small room with poor or no ventilation.

B. Assessments of consumer exposure

Estimating Exposure
The first step is usually a conservative theoretical calculation using reasonable worst-case assumptions and uncertainty factors. This can be done only after previous identification of the relevant product use scenarios (see part A of this annex – 'Factors influencing exposure') and assignment to them of appropriate model algorithms that allow quantification of exposure estimates. Details on how this can be done and specific examples are provided in the HERA risk assessment on the use of proteases in laundry and cleaning products (HERA 2005). If the conservative calculation using the highest likely exposure values indicates a potential for health effects to occur as a result of use of a product, then actual measurements should be considered (see below).

Measurements of exposure
Measurements provide a more accurate assessment of exposure and thus produce a more reliable basis for estimating the risk of using the product in question, especially in cases where estimated exposures exceed safe benchmark levels. Several parameters need to be considered to ensure that the new value being generated can be compared to established benchmark data. This includes how the enzyme protein exposures were determined for the benchmark that is being employed, as well as for the new product (for example, with regard to the analytical method and air sampling equipment used).

Examples of Airborne Exposure Measurement
Full details of example studies are included in the appendices of the SDA's 'Risk Assessment Guidance for Enzyme-Containing Products':
- **Appendix 1** Estimation of Exposure to Enzymes from Early Detergent Formulations
- **Appendix 2** Enzyme Risk Assessments of Hand Laundering Practices
- **Appendix 3** Spray Pre-Treater Case Study

The procedures used in simulating product use habits, air sampling, and measurements, as described in these studies, are good examples of how exposure can be determined for a product under consumer use conditions.