Industry Guidelines on the Safe Handling of Enzymes in Pulp & Paper Manufacturing

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This paper has been developed by the joint Enzymes Safety Working Group of:

AMFEP – Association of Manufacturers and Formulators of Enzyme Products www.amfep.org
CEPI – Confederation of European paper Industries http://www.cepi.org/

Any feedback on the content in this document is most welcome. Please contact the AMFEP or CEPI secretariats.

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List of Abbreviations:

ACGIH: American Conference of Governmental Industrial Hygienists
ADR: European Agreement concerning the International Carriage of Dangerous Goods by Road
AISE: International Association for Soaps, Detergents and Maintenance Products
AMFEP: Association of Manufacturers and Formulators of Enzyme Products
AOX: Adsorbable Organic Halides
APF: Assigned Protection Factor
BT: Brown Storage Tank
CAD: Chemical Agent Directive
CEPI: Confederation of European paper Industries
CLP: Classification, Labelling and Packaging (Regulation)
CSR: Chemical Safety Report
DMEL: Derived Minimum Effect Level
DP: Degree of polymerisation
ELISA: Enzyme-linked immunosorbent assay
ERC: Enzyme REACH Consortium
ES: Exposure Scenario(s)
eSDS: extended SDS
EU: European Union
FEDIMA: Federation of European Manufacturers and Suppliers of Ingredients to the Bakery Confectionary and Patisserie Industries
FEV1: Forced Expiratory Volume in one second
FVC: Forced Vital Capacity
GES: Generic Exposure Scenarios
GHS: Globally Harmonised System
HC: High Consistency/Density
HEPA: High Efficiency Particulate Air Filters
HRA: Health Risk Assessment
IBC: Intermediate Bulk Containers
MS: Member States
NIOSH: The National Institute for Occupational Safety and Health
OC: Operational Condition
OEL: Occupational Exposure Limits

PEFR: Peak Expiratory Flow Rate
PPE: Personal Protective Equipment
RAST: Radioallergosorbent Test
REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM: Risk Management Measure
RPE: Respiratory Protective Equipment
SDS: Safety Data Sheet
SDIA: Soap and Detergent Industry Association (UK)
SOP: Standard Operating Procedure
TMP: Thermo-mechanical pulp
TWA limit: Time-Weighted Average limit
ULPA: ultra-low particulate air filters
USA: United States of America

Forewords:

For decades, enzymes have been widely used in the pulp & paper industry due to their unique properties that facilitate the production of high quality pulp & paper products and, at the same time, significantly improve the ecological footprint of the produced products

Enzymes are proteins and, like other proteins, may act as respiratory sensitisers if individuals are repeatedly exposed to airborne dust or aerosols mist that contains them. Such sensitisation may ultimately lead to respiratory allergy, but it is important to note that not all individuals who become sensitised to enzymes develop allergy symptoms.
The risk of becoming sensitised at the workplace can, however, be effectively minimised by implementing risk management measures that aim to prevent the generation of airborne dust or aerosol mist. Risk management measures such as comprehensive process controls, smart product formulations, and functional handling instructions have all been shown to effectively protect the health of workers.

The Association of Manufacturers & Formulators of Enzyme Products (AMFEP) and the Confederation of European Paper Industries (CEPI) have jointly developed this guidance document for the safe handling of enzymes in the pulp & paper industry; thereby providing the insight and tools to help safeguard the health of the workers in this industry. To make the guidance document applicable to all sectors of the pulp & paper industry, some aspects of the guidance document have been kept generic.
It should be emphasised that whereas this guidance document covers the occupational conditions of the workers, end users are not in scope of this document.

This guidance document describes:

- Health hazards associated with enzymes
- Current regulatory framework concerning the use enzymes in the pulp & paper industry
- Management procedures required to ensure adequate controls and staff training
- Process and equipment design to minimise and maintain low exposure levels
- Air monitoring procedures to assess enzyme exposure levels
- Recommendations on health surveillance

The reader should keep in mind that this guidance document solely focuses on how to reduce airborne exposure to enzymes and, thus how to avoid respiratory sensitisation at the workplace. However, workers are typically exposed to numerous hazards at the workplace. To protect the health of workers, generally a thorough health risk assessment (HRA) is necessary for each workplace that addresses all hazards present at this workplace. Such a HRA may also need to include other hazards associated with (some) enzymes that are not addressed in detail this guidance document, such as skin irritation.

This guidance document reflects the state of technology and scientific understanding of controlling exposure to enzymes at the time of writing (2019). Therefore, the approaches described will be subject to changes as technical advances and scientific understanding improves.

Furthermore, only the control of enzyme exposure within the European pulp & paper industry has been addressed here. Although the general principles and recommendations are widely applicable, some of the guidance given may not be applicable to production sites in other parts of the world. Production plants outside of Europe must check if some elements in this guidance document are missing and/or in line with local regulation before implementing the guidance given.

Similar guidance documents on the safe handling of enzyme products are also available for the detergent[1] and the baking industry[2].

The creation of this document is based on a joint initiative by the AMFEP and CEPI, with substantial support by experts from Buckman.

[1] AISE: Safe Handling of Enzymes (Guideline, training materials, webinars): https://www.aise.eu/our-activities/standards-and-industry-guidelines/safe-handling-of-enzymes

[2] AMFEP, FEDIMA: On the Safe Handling of Enzymes in the Bakery Supply Chain (version 1, 2018): https://amfep.org/_library/_files/Industry_Guidelines_on_the_Safe_Handling_of_Enzymes_in_the_Bakery_Supply_Chain_-_MARCH_2018.pdf

1. Introduction

This guidance document focuses on safe handling of enzymes in the pulp & paper industry, i.e. how to avoid the formation of aerosols. In general, liquid enzyme products are used in this industry, products which are received, delivered within and into sealed systems such as pulp washing circuits, stock approach operations and whitewater circuits. The use of open circuits or the use of solid enzyme products are not considered best practice and are thus not covered in this guidance document. Should solid enzyme products be used, please contact your enzyme supplier for guidance.

The consequences of uncontrolled exposure to enzyme aerosols are well known, and the section below introduces enzymes and their benefits in the pulp & paper industry as well as the potential hazards associated with the handling of enzyme products. However, it is important to emphasise that when handled according to instructions and in well controlled industrial settings enzyme products can be used safely.

Enzymes are widely used in the pulp & paper industry due to their valuable and very specific properties; but what are they?

Enzymes form a special class of proteins being composed of the amino acid building blocks that are found in all types of proteins. Proteins are naturally produced by all living cells, and all living organisms – whether human, animal, plant or microorganisms – need enzymes to conduct virtually all the physiological processes which are essential for growth and life.

Enzymes act as catalysts: substances which, in very small amounts, are able to significantly speed up the rate of specific chemical reactions; for example, the building up or breaking down of organic matter such as carbohydrates, fats and other proteins. Enzymes are highly specialised in their functionality; with each enzyme acting only on a restricted number of substances, and only catalysing one specific reaction. For example, the starch degrading enzymes (amylases), present in human saliva break down starch into smaller molecules; which can then be degraded and absorbed when entering the gastrointestinal tract.

This specificity of enzymes makes them very useful in catalysing desired reactions in industrial processes. Consequently, enzymes are extensively used in several industries including in technical (e.g. detergent, starch, textile, pulp & paper and fuel alcohol), food (e.g. dairy, baking, brewing, wine and juice) and in animal feed arenas. Commercial enzyme preparations are produced by the carefully controlled fermentation of pure cultures of selected strains of non-pathogenic bacteria, yeasts or fungi.

Enzymes are grouped into several classes according to their activity: some of the most important classes to the pulp & paper segment and their contribution to manufacturing and finished product quality are mentioned in Table 1.

Table 1. Examples of Enzyme classes and corresponding functionalities in the pulp & paper industry. (Buckman, 2019)

No.	Application	Segment	Enzyme Benefit	Enzyme
1	Fibre modification	Chemical pulp & paper	Improved drainage, improved productivity, reduced use of energy, reduced use of chemicals, material mix optimisation, vessel element mitigation, improved strengthening potential	Cellulase
2	Biobleaching	Chemical pulp	Reduced use of bleaching chemicals and consequential AOX in effluents	Xylanase
3	Pulp modification	Chemical pulp	Degree of polymerisation reduction, pentosan reduction, extractives reduction, mannan reduction	Cellulase, Xylanase, Lipase, Mannanase
4	Anionic trash removal (TMP)	Mechanical pulp	Enhance the effectiveness of functional additives	Pectinase
5	Chip refining (TMP)	Mechanical pulp	Reduced use of energy	Cellulase, Laccase, Xylanase
6	Bleaching (TMP)	Mechanical pulp	Peroxide removal	Catalase
7	Pitch, stickies and deposit control	Mechanical and recycled pulp	Resin removal; boil-outs, improved processability of recycled pulp	Lipase, Protease
8	Deinking	Paper	Enables use of lower quality recycled paper	Cellulase, Amylase
9	Starch modification	Paper	Reduced viscosity	Amylase

For all enzyme classes the same principles apply regarding the safe handling of enzyme-containing materials used in the pulp & paper industry.

Hazards associated with enzymes

Industrial enzymes have a low toxicity in humans; i.e. enzymes present no concern for endpoints like acute toxicity, genotoxicity, sub-acute and repeated dose toxicity, reproductive toxicity and carcinogenicity. (1)(2)(3) However, like many other proteins, enzymes may act as allergens via inhalation. A two-step process has to take place for the development of an inhalation allergy: initial **sensitisation** followed by **elicitation.** (3)

Sensitisation: When allergens are inhaled in the form of dust or aerosols they may give rise to the formation of antibodies that are specific only to them. At this stage the sensitised individuals do not suffer from any allergic symptoms.

Elicitation: Sensitised individuals may then develop an allergy, if they are repeatedly exposed to sufficiently high airborne concentrations of the allergen concerned. (4) At this stage the individual will develop the symptoms typical for respiratory allergy such as hay fever. Some individuals may develop asthma upon continued exposure. When this condition is due to exposure in the working environment, it is called occupational allergy.

The respiratory symptoms from allergen exposure may include itching of the nose and eyes, nasal and sinus congestion and sneezing. Coughing, hoarseness, tightness of the chest and shortness of breath are all indicators of asthma. These symptoms may occur during or after working hours and they disappear within hours or a few days after the exposure has ceased. Allergy symptoms may be similar to those of the common cold, and if such symptoms occur frequently at the workplace and only rarely at weekends or during holidays, they may be the result of occupational enzyme exposure.

Allergy by inhalation caused by enzymes is similar to the respiratory allergies that are caused by well-known allergens like grass-pollen, house dust mites or cat dander; and the symptoms are similar. Some individuals are more prone to sensitisation than others are. Atopic individuals, i.e. persons already allergic to one or more of the common allergens, may develop an enzyme allergy more easily than others may. Not all atopic individuals will become allergic to enzymes and non-atopic individuals may develop an enzyme allergy if exposed to sufficiently high airborne concentrations on a regular basis.

Smokers have a markedly increased risk of becoming sensitised and developing allergy symptoms. (5) There is no scientific evidence that enzymes are associated with allergy caused by skin contact or ingestion. (6)(7)

In general, controlling enzyme exposure in pulp & paper manufacturing facilities will reduce the likelihood of work-related respiratory symptoms. Enzyme handling activities that may generate aerosols should be prevented to minimise the risk of exposures. This subject will be addressed in the following chapters of this document.

Experience from over 40 years of handling enzyme products in the detergent industry has proven that enzymes can be safely used in the workplace. This valuable experience and knowledge is now being applied to the pulp & paper industry to make it an even safer place in which to work.

References

1. Basketter, D.A., Berg, N., Kruszewski, F., Sarlo, K.S., 2012. The toxicology and immunology of detergent enzymes. *J. Immunotox.,* 2012; 9(3): 320-326
2. Basketter, D.A., Berg, N., Broekhuizen, C., Fieldsend, M., Kirkwood, S., Kluin, C., Mathieu, S., Rodriguez, C., 2012. Enzymes in cleaning products: An overview of toxicological properties and risk assessment/management. *Regulatory Toxicology and Pharmacology* 64 (2012) 117-123
3. Basketter, D.A., Broekhuizen, C., Fieldsend, M., Kirkwood, S., Mascarenhas, R., Maurer, K., Pedersen, C., Rodriguez, C., Schiff, H.E., 2010. Defining occupational and consumer exposure limits for enzyme protein respiratory allergens under REACH. *Toxicology* 268, 165-170.
4. Basketter, D.A., Berg, N., Kruszewski, F., Sarlo, K.S., Concoby, B., 2012. Relevance of sensitization to occupational asthma and allergy in the detergent industry. *J. Immunotox*., 2012; 9(3): 314-319
5. Johnsen, C. R., Sorensen, T. B., Larsen, A. I., Secher, A. B., Andreasen, E., Kofoed, G. S., ... & Gyntelberg, F. (1997). Allergy risk in an enzyme producing plant: a retrospective follow up study. *Occupational and environmental medicine*, *54*(9), 671-675.
6. Basketter, D. A., English, J. S. C., Wakelin, S. H., & White, I. R. (2008). Enzymes, detergents and skin: facts and fantasies. *British journal of dermatology*, *158*(6), 1177-1181.
7. Bindslev-Jensen, C., Skov, P. S., Roggen, E. L., Hvass, P., & Brinch, D. S. (2006). Investigation on possible allergenicity of 19 different commercial enzymes used in the food industry. *Food and chemical toxicology*, *44*(11), 1909-1915.

2. Regulatory requirements for Enzymes used in Pulp & Paper manufacturing in the EU

Ensuring workers' safety is a regulatory obligation for both enzyme suppliers and the pulp & paper manufacturers. Safety information on the use of enzymes must be communicated by the enzyme suppliers and the appropriate risk management measures (RMMs) and operational conditions (OCs) must be implemented by the pulp & paper manufacturers.

Exposure limits

Due to the risk of respiratory allergy, exposure to airborne enzyme dust or aerosols needs to be in control in the working environment. Two types of exposure limits are used for enzymes in the pulp & paper manufacturing:

Occupational exposure limits (OEL)
An occupational exposure limit of 60 ng/m^3 has been established for those enzyme products which belong to the protease class of Subtilisin. This OEL has been adopted as a regulatory exposure limit in many countries. See more details on this in Appendix 1, D of this chapter.

Derived Minimum Effect Level (DMEL)
For all enzyme products a DMEL of 60 ng/m^3 is now being used within EU in REACH dossiers. This means that airborne exposure to all enzyme products should be kept below this limit in occupational settings of the pulp & paper manufacturing.
See more details on this in Appendix 1, A and C of this chapter.

Safety communication from enzyme suppliers to the Pulp & Paper manufacturers

Safety Data Sheet and Exposure Scenarios
Enzyme suppliers must communicate safe use information via the Safety Data Sheet (SDS) under REACH. All applicable exposure limits should be stated in SDS (OELs and DMELs). Most enzymes used in pulp & paper manufacturing are to date registered under REACH. Thus, for substances that are marketed above 10 tons per year in the EU, the producer must make an extended SDS (eSDS) with Exposure Scenario(s) (ES) available. ES provide essential information on RMMs and OCs required to control enzyme exposure to humans and releases to the environment. If no ES are available in the eSDS, it is up to the end-user to determine the RMMs and OCs that are required to ensure the safe use of enzyme containing products.

Labels
Enzyme products must bear labels with hazard classification so that workers are aware of sufficient warnings. If an enzyme protein is above certain level (≥0,1%), a label clearly indicates that it contains enzymes as respiratory sensitiser(s) and additional pictogram and hazard/ precautionary statement at higher concentration (≥1%), of which criteria are set in CLP Regulation.

Implementation of safety measures by the Pulp & Paper manufacturers

Basic requirements for employers

Pulp & paper manufacturers have the obligation to implement RMMs and OCs aiming to protect the health of the workers. They must collect information – not only from SDS or labels discussed in the above section, but also other resources, such as from this guidance document and ensure that RMMs and OCs are in place that ensure the safe use of enzymes. This requirement is set under the Council Directive 98/24/EC, commonly known as the Chemical Agent Directive (CAD).

Exposure Scenarios (ES)

Once an ES in the eSDS is supplied to the pulp & paper manufacturers, they have 12 months to implement necessary measures as downstream users' obligation under REACH. If it is not possible to do so, they have several options for compliance, such as carrying out a downstream user assessment. However, it is recommended as a first step to contact the enzyme supplier to discuss possible solutions. The enzyme manufactures have a long history of working together with their customers to ensure the safe use of their products along the complete supply chain and welcome any initiative that improves the safety of workers handling enzyme products.

The following appendices provide detailed information on the above.

Chapter 2 - Appendix 1: Main regulatory requirements in the EU

A. EU REACH

Obligations of Registrants under REACH

Enzyme substances included in products destined for technical applications such as detergents, textile processing, biofuels, pulp & paper processing etc., need to be registered under the EU REACH Regulation[3] before they can be manufactured and/or imported into the EU in a volume above 1 ton per year. It lies with the manufacturers to register the substance under REACH and provide evidence that the substance can be used safely in all registered uses and along the complete supply chain. The European Chemicals Agency (ECHA) is the implementing authority on an EU level and supervises the registration process.

Activities regarding REACH implementation are discussed and facilitated within the Enzymes REACH Consortium (ERC) created by AMFEP. Since the third and final registration deadline of May 2018, most enzymes have been registered following the guidance documents developed by the ERC.[4]

If an enzyme is in the scope of REACH registration and has been registered in tonnages > 10 tons per year, then its registration dossier includes a Chemical Safety Assessment (CSA). The CSA consists of:

- Generic Exposure Scenarios (GES)
- Exposure estimation for the different routes of exposure under the conditions of use described in the GESs

[3] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

[4] http://www.enzymes-reach.org/content/welcome-enzymes-reach-consortium

- Risk characterisation; comparison of exposure levels to no or minimum effect levels.

GESs have been developed based on the knowledge available to the enzyme manufacturers about the different market sectors in which their products are used. Each GES defines the RMMs and OCs required to control enzyme exposure to humans and releases to the environment for one market sector. As the available computational tools for occupational exposure are not functional for respiratory sensitisers with very low limit values, measurements of airborne enzyme (active enzyme protein) at the respective workplaces are required for the exposure assessment.

In the case of enzymes, a DMEL of 60 ng/m^3 for occupational exposure has been proposed and is now being used in EU REACH dossiers for all enzymes. This DMEL has been established following a thorough retrospective review of occupational experience, correlating validated employee medical surveillance data against exposure records generated over an extended period (1).

Obligations of Downstream Users under REACH

The main obligation of downstream users under REACH is to comply with the information provided in the eSDS of the enzyme manufacturers. This includes information provided in the main body of the SDS, and OCs and RMMs defined in the ES, which are typically listed in the SDS Annex. ES may be missing if (1) the single substance or all substances in a mixture are produced/imported below 10 tons per year or (2) the formulator of a mixture decided to consolidate the safe use information of the different ingredients in the main body of the safety data sheet. If an end-user does receive a consolidated SDS for mixtures, it is legally possible to request the specific ES of each ingredient from the formulator.

It shall be noted that the main body of the SDS is considered a guidance document. Downstream users of enzymes, such as the pulp & paper industry, are, however, legally required to comply with the OCs and RMMs listed in the respective ES. The OCs and RMMs have been defined by the enzyme manufacturer in their ES to ensure safe use of enzymes (i.e. to keep exposure below the DMEL of 60 ng/m^3). If downstream users cannot comply or are unsure if they can comply with the OCs and RMMs laid out in the eSDS, then they are required to reach out to the enzyme manufactures and jointly work on assessing the workplace in questions and – if necessary – refine the respective ES. The enzyme manufactures have a long history of working together with their customers to ensure the safe use of their products along the complete supply chain and welcome any initiative that improves the safety of workers handling enzyme products.
Alternatively, downstream users can also carry out a “downstream user chemical safety assessment” and notify ECHA about this assessment.

Downstream users may be audited by National Inspectorates that have been identified by the national Member States (MS)[5]. These authorities have the authority to check if users of enzyme containing products comply with their obligation under REACH.

[5] https://echa.europa.eu/regulations/enforcement/national-inspectorates

It is important to note that downstream users are not directly required to assess compliance with the DMEL. They are solely required to comply with the OCs and RMMs that have been defined in the eSDS and to support manufacturers to define functional exposure scenario that allow the safe use of the enzyme products. Legally binding exposure limits are solely national OELs, which are discussed further down below.

B. CLP classification of enzymes and enzyme mixtures

The EU Regulation[6] for "Classification, Labelling and Packaging" (commonly known as CLP Regulation) adopts the United Nations' Globally Harmonised System on the classification and labelling of chemicals (GHS) across all European Union countries. The regulation requires companies to appropriately classify, label and package their substances and mixtures before placing them on the market. Since 1 June 2015, it is the only legislation in force in the EU for classification and labelling of substances and mixtures.

Enzymes may possess respiratory sensitisation potential regardless of the type of catalytic activity. Therefore, it is recommended classifying all enzymes as Respiratory Sensitiser Category 1 (H334) in accordance with the CLP Regulation, unless there is scientific evidence from e.g. immunochemical/immunological testing that they do not induce a specific response. CLP Annex VI currently includes a harmonised classification for 17 enzymes.

All these enzymes are classified and labelled as Respiratory Sensitiser Category 1 (H334): May cause allergy or asthma symptoms or breathing difficulties if inhaled. In addition to the Respiratory Sensitiser Category 1classification, proteases in Annex VI have additional classifications, namely STOT Single Exposure Category 3 (H335), Skin Irritation Category 2 (H315) and Eye Irritation Category 2 (H319) (except subtilisin, which is classified as Eye Damaging Category 1 (H318)). The REACH registration dossier for subtilisin includes additional self-classification as Acute Toxicity Category 4 (H302), Aquatic Acute 1 (H400) and Aquatic Chronic 2 (H411). These additional classifications are due to the proteolytic activity of proteases.

A mixture containing several enzymes must be classified as a respiratory sensitiser when at least one ingredient has been classified as such and is present at or above the appropriate generic concentration limits, unless sufficient data on the mixture itself indicating otherwise is available and bridging is not possible. Substances that are classified as sensitisers may elicit a response, when present in a mixture in quantities below the generic concentrations or specific concentration limits for classification, and must thus be indicated on the label at the lower concentrations established in Table 3.4.6 of Annex I to CLP.

Thus, for an enzyme (solid or liquid) that is a Respiratory Sensitiser Category 1 in a mixture, the general threshold concentration is 1% for the classification of the mixture (Table 3.4.5 of Annex I to CLP), and 0.1% for the inclusion of the supplementary statement EUH208 — *'Contains (name of sensitising substance). May produce an allergic reaction'* on the label (Table 3.4.6 OF Annex I to CLP). The threshold is considered based on active enzyme protein per individual type of catalytic activity.

[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

C. Worker's safety and obligations along the supply chain

The Chemical Agents Directive (CAD)[7] lays out provisions aimed at the protection of workers whose work brings them into contact with hazardous chemical agents. Under CAD, a substance is regarded as hazardous if it meets the criteria for classification as hazardous within any physical and/or health hazard classes laid down in CLP Regulation. Since most enzymes are classified as Respiratory Sensitiser Category 1, they are in the scope of CAD. There are no specific provisions for enzymes as a generic class of substances in CAD therefore enzymes are subject to the general provisions of this directive.

Where hazardous chemical agents are present in the workplace, employers must determine whether any risks to safety and health arise from their presence. The employer must be in possession of an assessment of the risk and this risk assessment must be kept up-to-date. The employer must take the necessary preventive measures to eliminate or reduce to a minimum the risks identified in the risk assessment following a hierarchy of prevention measures (described in Article 6 of CAD). Where this is not possible, the following shall be considered in order of priority:

i. design of appropriate work processes and engineering controls and use of adequate equipment and materials;
ii. application of collective protection measures at the source of the risk, such as adequate ventilation and appropriate organisational measures;
iii. where exposure cannot be prevented by other means, application of individual protection measures including personal protective equipment.

Directives are not implemented directly into national Member States (MS) legislation but set minimum standards which MS are required to reflect in corresponding national provisions. On this basis, employers operating within the EU that are fully complying with national workplace legislation should be managing the risks from enzyme and enzymes containing products according to these principles.

In addition, REACH regulation[8] requires demonstration of adequate control of risks for identified uses and exposure scenarios should be communicated to ensure implementation of risk managements throughout the supply chain. Enzyme manufacturers have developed GESs, containing information on the safe handling of enzyme products, which are communicated downstream via the eSDS. When downstream users receive an eSDS they must check that the GESs annexed to them cover their own use of the substance and their conditions of use or take alternative actions.

D. Occupational Exposure Limits

[7] Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC)

[8] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

Some few exposure limit values for enzymes have been derived by various groups and institutions. To understand their area of application, it is necessary to briefly explain two basic principles around exposure limit values:

First, the legal obligation: Generally, two types of exposure limit values exist. On the one hand, governmental (e.g. NIOSH, SCOEL) and non-governmental (e.g. ACGIH) institutes and groups may derive exposure limit values for chemicals that aim to protect workers, but which are not legally binding and predominantly act as guidance for risk assessors[9]. On the other hand, regulatory agencies (e.g. MAK Commission, HSE) may set exposure limit values that are legally binding and must not be exceeded. This type of exposure limit values is typically referred to as OELs, although no proper definition does exist. The European Standard EN689:2018 may be used as a basis to determine compliance with OELs.

Second, the exposure duration: Limit values are typically defined for an exposure duration of 15-minutes (often referred to as short-term exposure limit (STEL)) and/or 8-hour, but occasionally also other durations are used as benchmark (e.g. for enzymes sometimes 60-minute limit values exist). This means that the time-weighted average (TWA) exposure over the defined period may not exceed the limit value. Additionally, for some few chemicals, including enzymes, a so-called ceiling limit value has been determined by some countries. Such ceiling limit values are set where it is necessary to avoid transient excursions above the identified limit. If a ceiling limit value has been defined, then the exposure duration is irrelevant, and the exposure may not exceed the ceiling limit value at any time.

Currently, solely for the protease subtilisin OELs have been derived. In the early 1970's the American Conference of Governmental Industrial Hygienists (ACGIH) established a ceiling threshold limit value (TLV) of 60 ng/m^3 for the protease subtilisin. The ACGIH recommended limit has been adopted into national workplace legislation in several countries, in many cases as a ceiling limit (see Appendix 2). Some countries have also derived full shift exposure and/or short-term exposure limits, which are partly lower than 60 ng/m^3.

Although limits for other enzymes have not been established in national or EU-wide workplace legislation, the 60 ng/m^3 level is used by companies manufacturing enzymes and formulating enzyme-containing products as a benchmark applicable to all enzymes for their health risk assessments and to identify tasks where workers may need to wear respiratory protective equipment (RPE) to supplement the engineering controls that are in place.

[9] It shall be noted that several countries frequently use the recommended ACGIH values as basis to set their legally binding national OELs, such as Spain and Belgium. Additionally, the OELs recommended by SCOEL have often been used as basis to include these limit values in the Annex of the Chemical Agents Directive or Carcinogens at Work Directive.

Chapter 2 - Appendix 2: Examples of Subtilisin (Protease) regulatory exposure limits.[10]

Country	8-hr TWA limit (ng/m3)	Short-term limit (ng/m3)	Ceiling limit value (ng/m3)
Australia			60
Belgium	60		
Canada: Alberta, British Columbia, Manitoba, Ontario, Quebec			60
China	15	30	
Croatia	40		
Denmark	60		60
Finland	15		60
Iceland		60	
Ireland	60	60	
Italy			60
New Zealand			60
Singapore		60	
Spain		60	
Sweden	1 glycine unit/m^3		3 glycine unit/m^3
Switzerland		60	
USA-OSHA		60	
United Kingdom	40		

Chapter 2 - References

1 Basketter DA, Broekhuizen C, Fieldsend M, Kirkwood S, Mascarenhas R, Maurer K, Pedersen C, Rodriguez C, Schiff HE: Defining occupational and consumer exposure limits for enzyme protein respiratory allergens under REACH. Toxicology 268 (2010) 165–170.

[10] Information obtained from the GESTIS International Limits Values database (accessed on 31 May 2019) https://limitvalue.ifa.dguv.de/

3. Management and Training

In overall level, employers are always responsible for health and safety in workplaces. The health and safety laws apply to all businesses and those determine the basic precautions and responsibilities that applies to everyone. A significant part of this responsibility is **risk management** beginning with **hazard identification**. Every type of hazard which may be potentially harmful to employees must be identified, and suitable controls must be in place to mitigate those risks. The responsibility for providing a safe place to work is not only limited to employees but also includes other stakeholders such as contractors, cleaners, visitors and others who may be affected by their activities.

Even though management faces the majority of the responsibility for safe workplace provision, the participation of others should not be ignored. Full participation of all employees is the most effective way to create a safe working environment – whether with enzymes or any other potentially hazardous substances. Employees should be consulted in any decision-making process regarding risk management practices and solutions.

Risk management measures should always be based on a **hierarchy of controls**. This means that the exposure should primarily be prevented by eliminating or substituting the hazard. If this is not possible then exposure should be controlled by isolating the hazard or reducing it by means of engineering and/or design. In addition, administrative controls may be used such as the imposition of safe working practices & procedures. The final measure for reducing the exposure is the use of appropriate personal protective equipment (PPE).

Risk management processes must include the management of chemicals in the workplace. The **REACH Regulation (1907/2006)** requires that adequate control of risks to be demonstrated for identified uses of substances and gives a clear framework of precautions that must be in place before any kind of hazardous substances are used. Chemical manufacturers and suppliers must generate exposure scenarios for their end users. The exposure scenario contains the appropriate RMMS and OCs, which ensure that all the risks arising from the use of the substance can be controlled appropriately. A very good way of communicating chemical safety of each substance is the SDS. SDS must be kept in workplace and the content of those should be openly communicated to all employees who might be affected by those.

Safety management in the workplace should cover near miss and accident investigations, and reporting procedures for these events. Learning from such incidents is a key element for the development of a safer workplace for everyone and this can be achieved by reviewing every significant near miss or accident. The outcomes of investigations inform future risk assessments and corrective actions to prevent similar incidents happening again.

Training is a key element for raising the awareness, competence and knowledge about safety matters. All employees must have basic training in general health and safety in addition to their task specific training to gain professionalism. All workers handling chemicals and especially enzymes should also have training in the potential hazards arising from different chemicals used (such as enzymes) and the appropriate precautions to take when working with these substances. Training must also be organised for others who may be exposed on site (such as maintenance personnel, external contractors etc.), and should include background information

on hazards, standard instructions and emergency instructions. Everyone attending the site for the first time should be informed and/or trained about the basics of chemical safety during their introduction. Training should then be continued over time on a regular basis, and always when significant changes to processes or chemicals used are made.

From the health perspective, it is important to inform everyone who might be exposed about hazards, such as respiratory sensitisers. For example, standard operational procedures should be communicated to all staff so that they understand how, as well as why, they should avoid any unnecessary exposure. Even small things such as the correct way to handle empty chemical containers can make a big difference. Other important training subjects include possible symptoms of respiratory allergy, correct handling of spillages and cleaning situations as well as emergency situation procedures.

After basic training has been covered, more task specific training should be given. This should also cover the usage and maintenance of **PPE**: for example, how to dress, undress and contain PPE's properly; and the key elements of how to maintain PPE's; including cleaning and checking their condition for wear and tear. Following the basic training for PPE it is essential for everyone to have the opportunity to test the effectiveness and the actual level of protection that the equipment gives. This can be done by fit testing of RPE and practice in a controlled environment.

The company's training program should be reviewed regularly and always when significant changes are made to its processes. Risk assessments should also provide new material for training when something new is observed or something has changed in the process. Investigations of accidents and near miss situations should contribute to the content of training to ensure that lessons are learned.

Documenting the delivery of all training is as important as the monitoring of its comprehension. Verifying the effectiveness of every step of risk management controls is always important, but it is vital for discerning the best ways to develop them further. For example, it is good practice to collect feedback about the content of training immediately after the event in addition to collecting it at a later date, once the new knowledge has been in use.

Documentation should be extended to standard operating procedures (SOP's), which are clear and easy to be understood. SOP's are meant to describe the right way of working in each task to ensure safety and effectiveness. The risk assessments in workplace should also develop these SOP's to cover the risks present. As systems and methods of working continually evolve, it is vital that SOP's are periodically reviewed to ensure that they are still relevant and fit for purpose. It is also important to ensure and monitor that workforce continually adhere to those.

AMFEP and CEPI strongly encourage every vocational **school and university** providing training in pulp & paper industry throughout Europe to include training about chemical safety including enzyme related hazards in the curriculum. Knowledge about the hazards present in the industry and the control measures used to manage risks should be introduced as early as possible for every person starting in the industry.

4. Control of Exposure during the Handling of Enzymes in Pulp & Paper Manufacturing

4.1. Introduction

The intent of this chapter is to prevent operator exposure to enzymes, via inhalation, during the manufacturing process of pulp & paper.

To prevent the exposure of employees to enzymes during the manufacture of pulp & paper products, there is a series of well-established engineering controls and operational procedures that have been developed over many years by different industry sectors and which are now considered best practice. They are complementary elements, and each element should be in place if proper control is to be achieved.

The key strategies are:

• The prevention of aerosol formation from enzyme liquids by the proper plant design to prevent or minimise the formation of aerosols when using enzymes in the pulp & paper manufacturing
• The containment at source of any liquid aerosols that may be produced during handling by using closed process equipment, or enclosed equipment maintained under negative pressure by ventilation control
• The avoidance of any routine or uncontrolled spillages of enzyme-containing material, including from waste and packaging
• The clean / hygienic design of plant and equipment

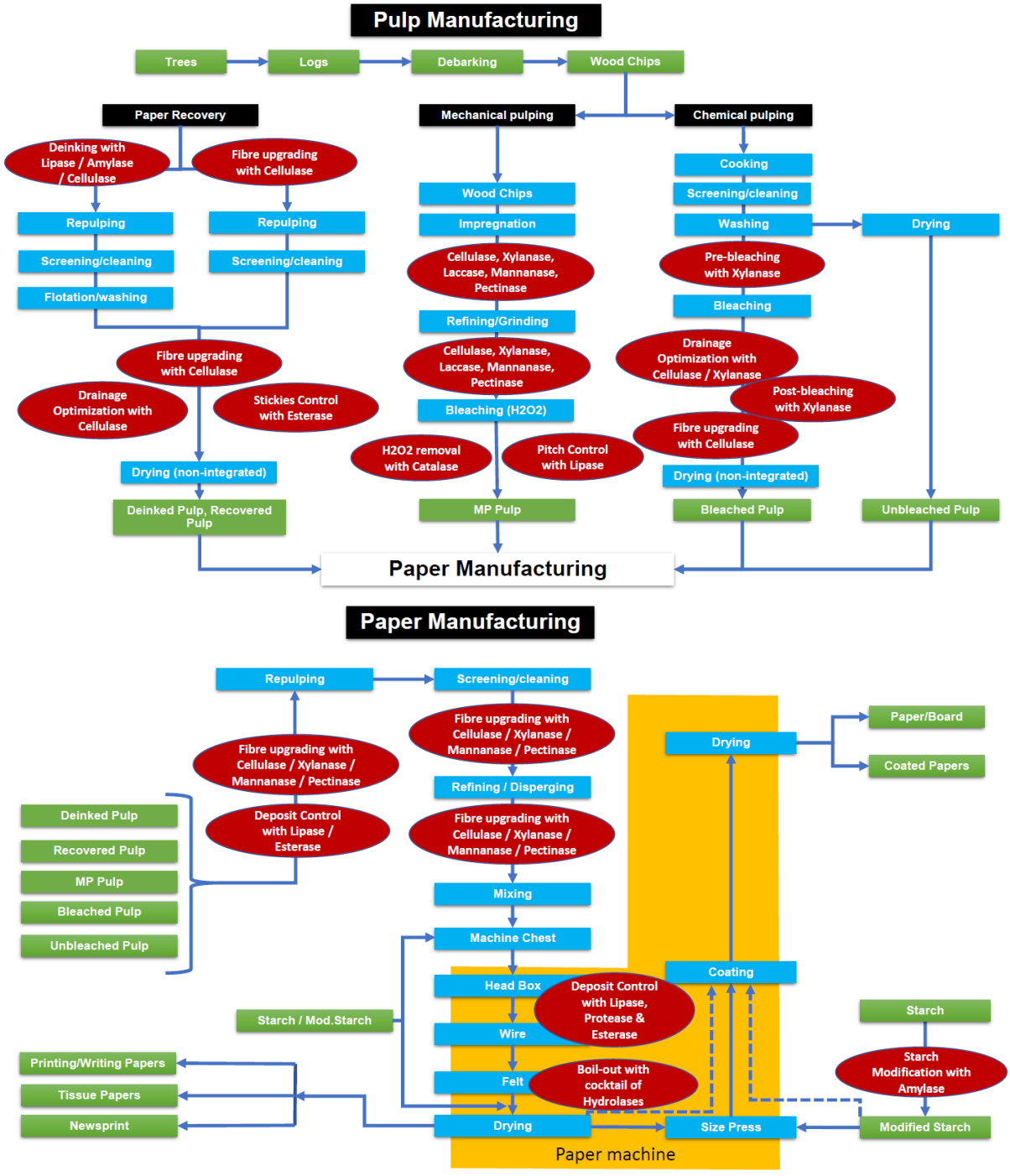
4.2. Enzymes Quality and Form

The main form of enzyme products supplied are enzyme liquids (most common in pulp & paper industry)

Powdered enzymes are recommended not to be used due to the higher risk of enzyme dust generation.

For liquid enzymes it is important to avoid aerosolisation, including spraying the liquid enzyme, vigorously splashing the liquid enzyme product, or cleaning up spills using high pressure washing.

4.3. The use of Enzymes in Pulp & Paper Manufacturing



In the flowcharts above, examples are given for which purposes enzymes could be used.

4.4 Enzyme Exposure Scenarios in Pulp & Paper Manufacturing

Areas of potential contact between enzyme products and operators are:

- Disposal of empty supply units (further explained in Chapter 4.5.3)
- Discharge of supply units (4.7)

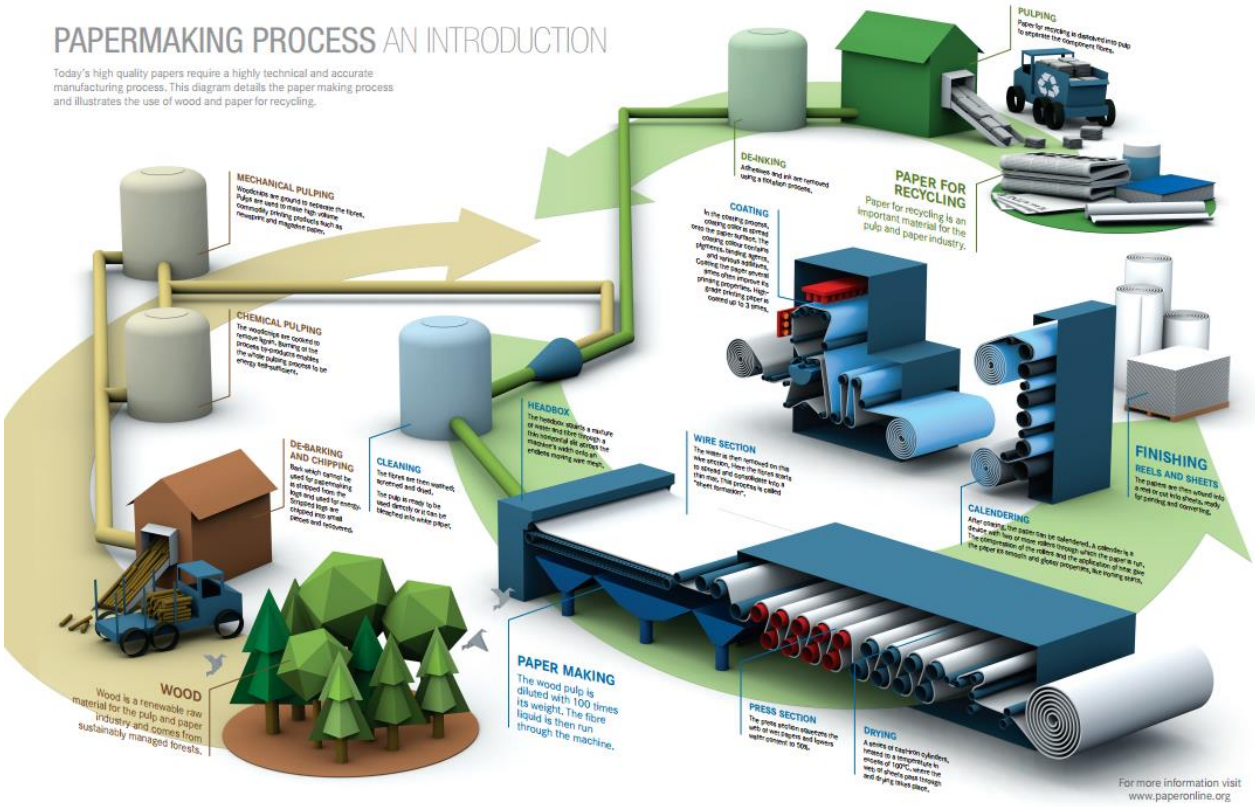
- Enzyme Transfer and Dosing (4.8)
- Enzyme Handling Plant and Equipment (4.9.1)
- Dealing with Spillages, and Cleaning of Plant and Equipment (4.10)

The recommended use of PPE is explained in Chapter 4.11

Some general principles

- Pulp & paper enzymes are provided as a liquid formulation, and are generally applied through dedicated tubing, valves and fittings into the dilution waterline to the suction side of transfer pumps. Transfer pumps will ensure good mixing of the enzyme within the stock.
- It is preferred not to apply enzyme into the top of a chest, which could lead to enzyme pooling and/or poor mixing.
- Enzymes are not recommended for surface treatment and therefore any type of spray application should not be utilised.

The following picture shows a general layout of an integrated pulp & paper manufacturing mill with all major unit operations. This generic process will differ from mill to mill but the basic process steps are shown.



Courtesy: CEPI

Enzyme applications and their potential dosage areas are indicated in the two flowcharts above; the first flowchart for making the pulp and the second flowchart mentioning more potential enzyme applications.

A somewhat different layout is seen in paper mills using paper for recycling as fibre raw material; here the process starts with the paper mills´ stock preparation by pulping and de-inking of the recovered fibres. A common enzyme addition point would here be the pulper.

The specific enzyme applications are explained in the below chapters 4.4.1 (Pulp mill applications) and 4.4.2 (Paper mill application).

The starch preparation unit applies enzymes usually in a place separated from the paper line.

4.4.1. Enzymes for pulp applications: see 'Pulp Manufacturing' flowchart above

Enzymes have been developed and applied to improve the bleaching of the chemical pulp since the 1980's. Benefits have been documented in pulp mills employing both Elemental Chlorine Free processes applying Chlorine Dioxide and Totally Chlorine free processes applying Hydrogen Peroxide and/or Ozone.

The enzymes are supplied in liquid form and stored in closed containers, which minimises or eliminates their potential release into the surrounding environments where operators or workers could be found. Before the enzyme is added into the process, these containers are connected directly into the enzyme dosing metering system and this dosing system is also connected directly into the addition point in the bleaching plant. The enzyme is thereby isolated from the working environment in a closed piping system and this from enzyme storage to addition point in the process.

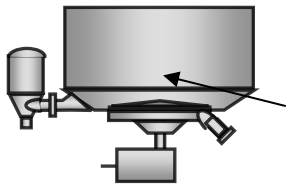
The enzyme(s) can be added at different locations within the pulp mill depending if they are to be used to augment bleaching or as a drainage aid for the pulp dryer. For the bleaching of pulp, the enzyme is added before the bleaching plant into the High Consistency/Density Storage tower (also known as Brown Storage tank (BT) or Unbleached Storage tank). The enzyme is thoroughly denatured/inactivated during the following bleaching stages.

As a drainage aid, the enzyme is added after the bleaching plant into the Bleached High Density/Consistency (HC) Storage tower (also known as Bleached Storage tank). Here it is recommended to check inactivation conditions for the enzyme by securing high enough temperatures during pulp drying.

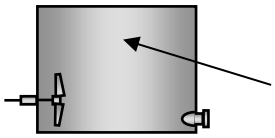
4.4.2 Enzymes for paper applications: See Paper Manufacturing flowchart above

Enzymes have been used in paper making for decades for starch modification, de-inking, deposit control, etc.

The enzyme(s) can be added at different locations within the paper mill, they are dosed as early as possible in the process (e.g. the pulper of a non-integrated mill) in order to allow maximum contact time of enzyme and fibre. Alternatively, they can be dosed into one of the following chests. Dosing into an open pulper or chest should be avoided when possible. Otherwise, it is necessary to ensure that aerosolised enzymes are not being released.
The enzyme is usually denatured/inactivated during the paper drying stages.



Low Consistency Pulper
4-5% Consistency
Liquid Enzyme



Chest (Refiner-/Storage-/Machine-/etc.)
4-5% Consistency
Liquid Enzyme

Picture: Direct dosage of enzyme into the pulper (no enzyme exposure). Courtesy of Buckman

4.5 Supply Units

4.5.1. Types

Liquid enzyme formulations for the pulp & paper applications are available in 3 main supply units.

4.5.1.1. Jerrycan or canister

Packaging size (L)	Depth (mm)	Width (mm)	Height (mm)	Container weight (kg)	Example
25 - canister	290 - 302	252 - 264	457 - 469	1.2	
Material		Dimensions (mm)			

Screw cap, type 61, heated foil seal	Outer Ø 57.5 - 60.5, Inner Ø 47.0 – 50.0, Height 21.4 – 23.4	

4.5.1.2 Drum

Packaging size (L)	Depth (mm)	Width (mm)	Height (mm)	Container weight (kg)	Example
220 - drum	Ø 578 - 584		930 - 940	8.5	
Material			Dimensions (mm)		
Drum compliant with DIN ISO 20848-2, Bung closure system compliant with DIN ISO 20848-3			BCS 70x6 plastic seal (delivered detached from drum) inner Ø 57.3, BCS 56x4 aluminium seal (sealed) inner Ø 52.9		

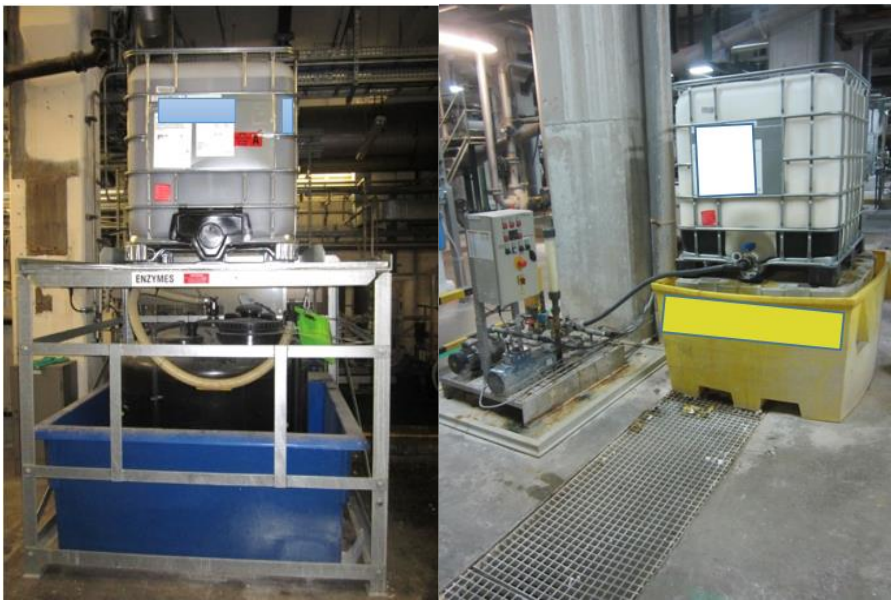
4.5.1.3 IBC

Packaging size (L)	Depth (mm)	Width (mm)	Height (mm)	Container weight (kg)	Example
1000 - IBC	1200	1000	1160 (incl. pallet)	55.0	
Material			Dimensions (mm)		
Filling opening: Screw cap HDPE / O-ring gasket TPE, Discharge opening: HDPE/PP/aluminium film (sealed)			Filling opening Ø 150, Discharge opening Ø 50, Fork opening Ø 100		

4.5.2. Storage of Supply Units

All supply units should be stored in the warehouse on pallets for ease of handling.
32 Jerrycans or 4 drums can be put on 1 pallet. Smaller pallets exist where for example only 2 drums fit on. Plastic film is wrapped around the smaller supply units for transportation. The European law for road transport dictates it as such (ADR/Directive 2008/68/EC).
It is a good practice to put maximum 3 IBC's on top of each other. Please consult your IBC supplier for further guidance.
Please see picture below:

Mother Daughter decanting system and containment bund:
The mother daughter is a system that guarantees the continued supply of enzymes by ensuring that the black container is always refilled with the products. The IBC container on top is replaced when empty.



Picture: IBC with containment bund

4.5.3. Disposal of Empty Supply Units

Jerrycans are normally disposed at the end-users site.

Drums might or might not fall under the recall policy; if yes, they are taken back and rinsed.

IBC's have a special recall policy, so-called "reverse logistics". With every IBC delivered, documents are attached for the end-user with instructions what to do in order that a disposal company come to pick them up. Some disposal companies only reuse the metal frame and the plastic container is disposed and replaced by a new one.
Third-party waste recycling companies should be informed of the hazards and risks associated with the handling and processing of packaging that is potentially contaminated with enzyme product in order to control the exposures, especially when cleaning the IBC's. Operators should be trained and wear the appropriate PPE.

Please follow local regulations as they may differ from country to country.

4.6 Building and Plant Design Considerations

4.6.1 General Principles

Buildings and plants should be designed to the extent possible to provide an environment that is easy to maintain in terms of hygiene and which minimises the generation of aerosols by avoiding spraying, splashing, or spillage.

Therefore, it is essential that clean design principles be used for buildings.

4.6.2 Buildings

Walls should be smooth, and sealed (e.g. painted), or clad in a smooth material that is easy to keep clean. Fittings such as shelves, cupboards, etc., should be kept to a minimum and be positioned such that they can be easily cleaned. Old fittings and fixtures that are no longer in use should be removed.

Ceilings should be smooth and give easy access for periodic cleaning.

Floors and stairs should be easy to clean.

Windows: complex window frames should be avoided, as these are difficult to keep clean.

Ductwork should be tubular shapes

4.6.3 Equipment

Enzyme liquids have a significant potential for aerosol formation during handling and a risk

of dust generation if spillages are left to dry out. The process and packing equipment should be designed to control this additional risk by effective containment of liquids, i.e. no leaks, and by minimising the chance of spraying and/or splashing of liquid.

The largest potential source of personal exposure to enzyme aerosols is the storage and refilling equipment for the enzyme dispersion. Interface and frequency of exposure should be eliminated or reduced as follows:

The design should prevent external spillage and spattering of fluid by:

- Limited drop heights and avoidance of splashes of liquids on surfaces [including liquid surfaces].
- Design of efficient enclosures to completely recirculate spilled liquid splashes
- Spill trays to completely collect and return the spilled material.
- Suitable sampling points
- Efficient machine setup to avoid frequent interruptions and manual intervention
- Using CIP technologies [Cleaning in Place]

In places where spills are evident or routine and have not yet been disposed of, drip pans should be provided for product removal.
The design should avoid or reduce spills, thus reducing the need for frequent cleaning of spilled material.

4.6.3.1. Liquid Handling/Transfer Equipment

Pipes

Rigid pipes should be leak free. Welded joints are preferred. Other options are compression joints and flanges. If flanges are used, these should be covered with a flange protector to prevent the development of sprays if the flange/seal fails. Flexible pipes for unloading should be robust enough to withstand abrasion and bending. Couplings for flexible discharge lines should be dry-break or cam-lock type to prevent spillage from pipe work that is disconnected.

Pumps

Preferred pumps for transfer and dosing are based on a leak free mechanical seal design, i.e. magnet drive or sealed motor and pump combination. Please refer to Chapter 4.8.1., under ‘best practice’.

Tank Vents

Displaced air from enzyme storage units that is vented back into the work place must be controlled by HEPA filtration. Air vented outside should be vented away from any intake air, and can be done without filtration.

Valves

Valves should have leak free seals. Those connected to the pipe or pump with flanges should be covered with flange protectors to prevent the development of sprays if the flange/seal fails.

4.7 Discharge of Supply Units

In general, best practice when designing a safe discharge system for enzymes is to completely isolate the operator from the enzyme raw material. There should be no direct interface between the operator and the raw material. Supply units should be coupled and sealed directly to the discharge equipment to ensure this. The process should be undertaken in an area that can provide a high level of containment and control, in case a spillage, or release, should occur. Finally, all operators in the discharge area should be provided with, and wear, suitable respiratory and personal protective equipment as secondary protection, as in the event of a spillage or release of enzymes in this area, it is likely that a peak exposure will occur. Personal and respiratory protection is discussed in detail in section 4.11.
As discussed in 4.2 and 4.4, we will focus on the handling and dosage of liquid enzymes.

4.7.1 Isolation of Discharge Process

The best practice for discharge of supply units is to locate the discharge equipment within a containment area, or booth, designed specifically for the handling of hazardous materials. The area should have a high air change rate to effect rapid dilution and removal of any aerosol in a direction away from the operator's breathing zone, and without allowing the aerosol to settle. Turbulent airflow should be minimised to ensure effective control and removal of airborne contamination.

An example is the use of a laminar downflow booth [**Appendix 1]**. These provide a high level of containment through use of laminar downflow air, and a high rate of air change (800/hr.) recirculated through high efficiency (HEPA) filtration.

Another example is the location of the discharge equipment within an enclosed room, or booth, that is maintained under negative pressure at all times, with an inward air velocity of $\geq$ 1.0 m/s at all gaps or openings that lead to the outside of the room or booth [for example gaps around doors of transfer pipework], and good air change rate (e.g.$\geq$ 10 air changes per hour). This will ensure that any airborne contamination is maintained within the room, or booth, but this system is less efficient than a laminar downflow booth at removal of airborne contamination or preventing aerosol from settling out.

In either case, local exhaust ventilation at the discharge point may be required to prevent the release of dust or aerosol if the supply unit is not directly coupled to the discharge equipment. This is discussed in more detail in the following sections.

Whichever system of discharge is in place, it should be ensured that empty supply units are externally clean (i.e. not contaminated with dust / enzyme) and / or contained before they are moved away from the isolated discharge area. Contaminated materials and the disposal of empty supply units should be handled as detailed in Section 4.5.3.

4.7.2. Discharge of Intermediate Bulk Containers (Rigid)

This type of rigid IBC is more commonly used for liquids. Discharge of liquids is normally via direct connection of pipe work to the valve on the front of the IBC.

Liquids IBCs may be discharged into a variety of holding tanks, hoppers, weighing vessels etc., or may be used to dose directly into a continuous process. In any event, the IBC should be coupled to the process using a dry-break or cam-lock type coupling to avoid any spillages during the coupling / de-coupling operation. The cap on the top of the IBC should either be vented, or should be loosened slightly to allow air to enter during the discharge operation. As air will be drawn into the IBC during discharge, and will not be expelled, there is no need to incorporate filtration into this vent. If the IBC can vent into the room, a cap incorporating a HEPA filter can be installed to prevent the release of aerosols.

The discharge areas - whether a downflow booth, or enclosed discharge room - should be provided with suitable secondary containment to contain gross spillage of enzymes in the event of a failure of the IBC, or associated pipework. This may be in the form of a physical barrier to maintain the spillage within the controlled area, or a closed drainage channel to prevent liquid leaving the controlled area and to safely direct the spillage to an intermediate holding tank incorporating suitable venting facilities to prevent the escape of aerosol.

Picture: IBC with liquid enzyme on their secondary containment; example of mother- daughter decanting system

4.7.3. Discharge of Drums

Metal or Plastic Drums for Liquids

As with rigid IBCs, drums should be discharged from within the controlled discharge area, using dry-break or cam-lock type couplings fitted to the threaded opening in the drum lid.

Once the first half of the dry-break coupling is fitted to the top of the drum, the drum will need to be positioned on its side in a purpose-built cradle, which is slightly sloped forwards to ensure that the contents are emptied effectively. If a cam-lock coupling is used, a shut off valve will have to be fitted before the drum is positioned in the cradle.

Drums may then be discharged by use of pumps. The use of dip-pipes or removable “Drum pumps” is not recommended. These are prone to cause spillage and personal contamination on removal from the drum and during storage when not in use. This is further handled under 4.8.

As with liquids IBCs, the controlled discharge area should be surrounded by secondary containment to contain gross spillages.

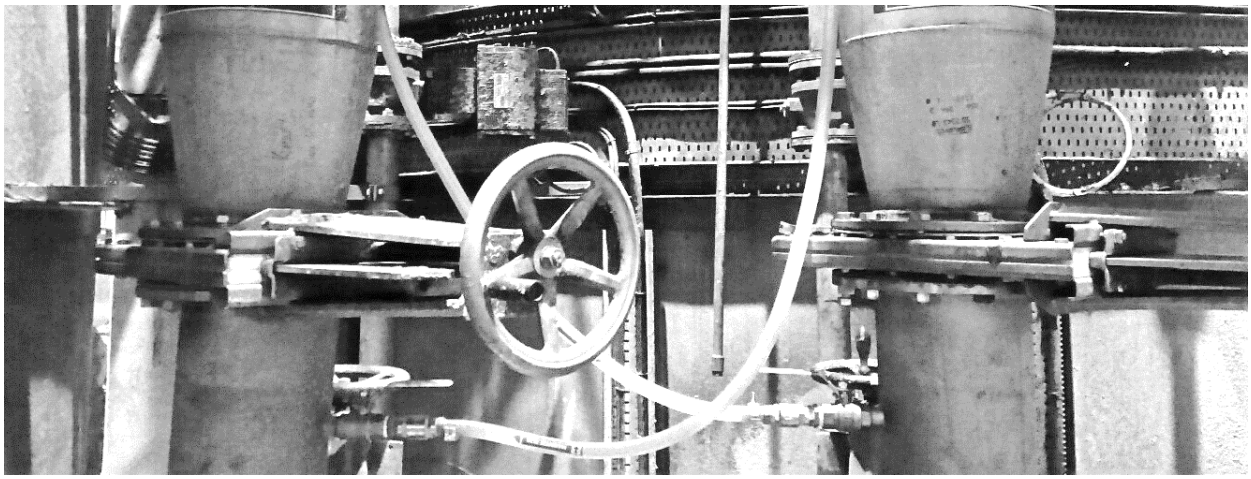
4.8. Enzyme Transfer and Dosing

In plants, where the process layout is relatively simple, transfer of enzyme liquids may be achieved by gravity. In some plants, a combination of gravity and powered systems may be required, and in others, enzyme transfer may be solely by pumps.

In any case, containment should be implemented to avoid the release of enzyme aerosols. Containment can be achieved by two means:

- Complete enclosure – a physically sealed / closed system
- Partial enclosure and ventilation control

Dosing should only be carried out using contained and controlled dosing systems.
As stated under 4.7, and as a general advice, the best practice when designing a safe discharge system for enzymes is to completely isolate the operator from the enzyme raw material, with no direct interface between the operator and the raw material. Supply units should be coupled and sealed directly to the discharge equipment to ensure this. The process should be undertaken in an area that can provide a high level of containment and control should a spillage, or release, occur.



Picture: dosing directly into the pipes; see also picture under 4.4.2: dosing directly in the pulper. (Courtesy of Buckman)

4.8.1. Dosing of Liquid Enzyme

As a general advice, 'manual dosing' of liquid enzymes must not be carried out by open pouring through the manway, or over the side of any vessel.

Continuous Manufacturing Plant

Continuous dosing plants bring together two or more metered streams of liquid and mix them together. Typically, a continuous enzyme dosing facility injects enzymes into the pulp stream. The enzymes may be pumped directly from a supply IBC.

Liquids dosing plants are quite complex, often pressurized, and there are many points at which leaks may occur. Therefore, it is recommended that the location where enzymes are dosed in an open way be sited in a contained [authorised access] area under negative pressure to maintain an inward airflow of 1.0m/s, and with a 'good general ventilation' (3 to 5 air exchanges per hour).
https://echa.europa.eu/documents/10162/13655/du_practical_guide_13_en.pdf/2c3bc624-fb3c-4515-a581-87b79d460d38

Access to the dosing area should be restricted to authorised employees, wearing respiratory protection as secondary protection in the event of a failure. The area should be kept dry to

aid the visual detection of loss of containment.

Batch Manufacturing Plants – Automated dosing

Liquid enzymes may be added to a batch-mixing vessel or directly into the process. Typically, batch-mixing vessels have a man way that can be opened either to observe the product, or to take samples for analysis. It is at this point that there is a risk of exposure to enzyme aerosol from the liquid enzyme. To avoid exposure the following should be in place:

- The mixing vessel should be under the control of exhaust ventilation to achieve a recommended air velocity across [or into] the man way of > 1.0 m/s
- Enzyme dosing and mixing should only take place with the man way in the closed position. Ideally dosing and mixing equipment should be interlocked with the man way
- Enzyme should be added tangentially, or down the side of the mixer wall to reduce the potential for generating aerosol from splash filling

Ideally, the mixing vessel should have no access points, or hatches, that can be opened during normal operation, and the vessel should be effectively sealed.

Underneath practices may occur:

1° Bad practice: manual dosing of liquid enzymes, with direct interface between the operator and the raw material

'Manual dosing' of liquid enzymes must not be carried out by open pouring through the manway, or over the side of any vessel. The potential for exposure to aerosol from spillage or from personal contamination is too high using a manual method. From experience it is known that this practice could result in enzyme airborne levels significantly above the DMEL of 60 ng/m³.

2° Better practice, when using manually operated dosing systems, reducing the potential of direct interface between the operator and the raw material.

Manual dispensing of enzymes may be achieved safely but requires a high level of engineering control, along with a high quality of personal and respiratory protection.

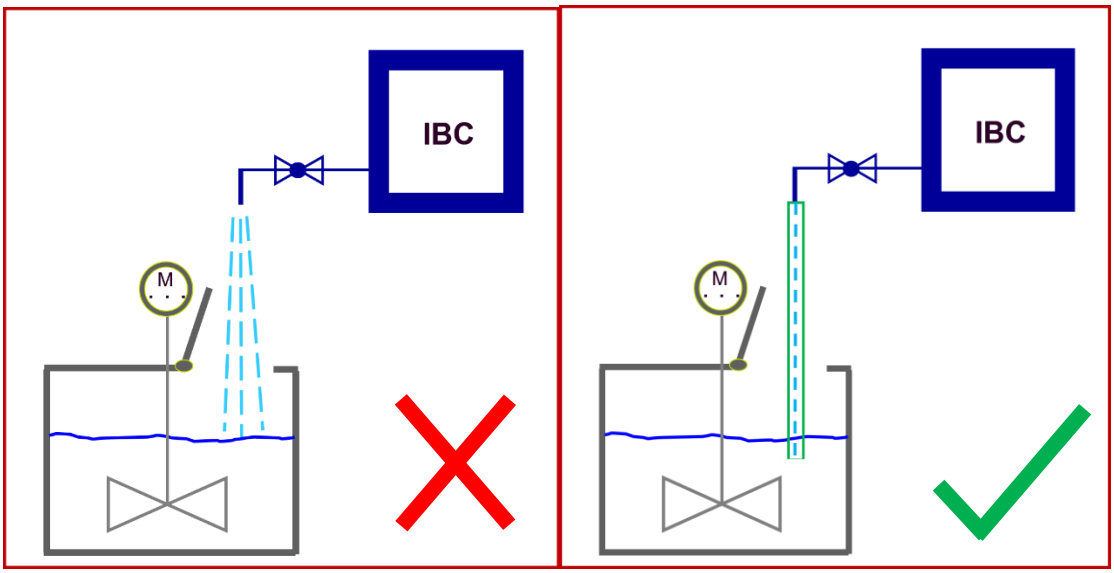
The need for the following should be evaluated:
• An isolated dispensary for weighing out enzymes
• Suitable transfer containers
• Local exhaust ventilation at the dispensing station
• Direct coupling of the transfer container to the process
• Positive pressure respiratory protection
• Protective overalls
• Proper handling of spillage

It is essential that the supply units from which enzymes are to be dispensed are suitable for the purpose, and are in a fixed position from which the contents can be dispensed safely. The operator should not dispense the contents of the supply unit by direct tipping /pouring, which could result in the spillage of the complete contents of the supply unit.

As with rigid IBCs, drums should be discharged from within the controlled discharge area, using dry-break or cam-lock type couplings fitted to the threaded opening in the drum lid, as described under 4.7.3.

The use of dip-pipes or removable "Drum pumps" is not recommended. These are prone to

cause spillage and personal contamination on removal from the drum and during storage when not in use.



However, when necessary, the situation as described in the picture above, could be made much safer if the outlet of the IBC was provided with a flexible tubing, ending up under the surface level of the liquid, in this way preventing splashing of the enzyme liquid. In this situation, enzyme air monitoring has shown results that were below the DMEL of 60 ng/m³. Care should be taken to avoid exposure when removing and storing the flexible tubing from the drum.

3° Best practice: automated dosing in Batch or Continuous Manufacturing plants

Liquid enzymes may be added to a batch-mixing vessel, or even better, directly into the process.

Preferred pumps for transfer and dosing are based on a leak free mechanical seal design i.e. magnet drive or sealed motor and pump combination. Pneumatic pumps are used but exhaust air must be vented outside the building away from any air intakes or filtered through a HEPA filter prior to discharge. Isolation valves should be fitted to the feed and delivery side of the pump for spill free removal during maintenance.

Single diaphragm pumps used for liquid enzymes should only be used if the exhaust air is vented to the outside (away from any intake air) as minor faults in this type of equipment can generate significant aerosol concentrations in the exhaust air. Some types of air driven multiple diaphragm pumps may be acceptable, as there is a far lower probability that multiple diaphragms could fail at the same time. The use of these should be backed up with regular maintenance to ensure reliability, and the use of a detection system to detect a faulty membrane. In addition, there must be no likelihood that product could contaminate the compressed air exhaust.
HEPA filters may be used as a secondary protection on the air exhaust.

An example of liquid enzyme transfer pumps is shown in the figure below.

Figure: Example of Enzyme Transfer Pump Sets (source: AISE: Guidelines for the Safe Handling of Enzymes in the Detergent Manufacturing)

4.9. Ventilation efficiency and recommendations

Disclaimer: requirements may vary from country to country; companies need to check the legal requirements, which are applicable in their region.

The treatment of extraction air contaminated with enzyme dust and/or aerosol will depend upon the type of plant and/or equipment that is under control, the degree of contamination, and the location into which the extract air is discharged. Most countries already have legislation concerning the concentration of particulates that can be discharged to the external atmosphere. Legislative requirements regarding venting of exhaust air should always be adhered to first, followed by the guidance in this document.

4.9.1. Enzyme Handling Plant and Equipment

Most local exhaust ventilation systems are directly exhausted outside in accordance with local environment emission regulations and in a location, which prevents intake back into the building. However, if the local exhaust ventilation discharge is purposely recirculated back into the workplace, then extra filtration is needed to prevent the discharge of enzyme dust and/or aerosol back into the working environment. In this case, the minimum standard of filtration is considered to be HEPA filtration, to at least H14 (EN1822).
The International Standard EN 1822 has revised filter classifications; the recommended finishing filter class for enzymes is now H14, formerly known as class EU13 and you may still see this on some older stock or products.

HEPA filters are normally preceded by one or two pre-filters to remove the bigger particle sizes, preventing the HEPA filter from blocking up, and thus prolonging the HEPA filters operating

life. This is typical of the filtration necessary for a laminar downflow booth, which re-circulates air to the working environment **(Appendix 1).**

Depending on the expected dust loading, the equipment suppliers can recommend suitable pre-filters, but a typical three-stage system would be comprised of the elements in the following table:

Filter Type	Classification	Efficiency
Pre-Filter	G4	95% @ 10 µm
Fine Dust Filter	F8	90 – 95% @ 5 µm
HEPA Filter	H14	99.995 – 99.9995% @ 0.3 µm

4.9.2. Re-Circulated Air Systems

It is not recommended that air from enzyme-controlled systems is re-circulated to the working environment.

Air that is to be returned to the working environment for example from a down flow booth must be filtered to HEPA standard, to at least H14 and must be appropriately validated. In North America, there is a specific consensus standard called ANSI/AIHA Z9,.7-2007 (Recirculation of Air from Industrial Process Exhaust Systems). This consensus standard provides design and operational requirements for the recirculation of exhausted air from systems, which require special precautions like enzymes.

Filtration systems used for this purpose should be monitored for performance via the use of static pressure gauges, which will alarm in the event of a filter failure. Taking regular readings from such gauges can be part of the plant monitoring systems.

Relatively inexpensive dust penetration detection instruments are also available to quantify the amount of dust that passes a filter. However, these are not appropriate for liquid aerosols.

4.10. Dealing with Spillages, and Cleaning of Plant and Equipment.

The use of improper or improvised clean-up methods can result in generation of airborne enzymes. This can result in the exposure of operators in the immediate area of any cleaning operation and in adjacent areas via general ventilation. Clean-up operations are a significant potential source of peak enzyme exposures, which need to be managed by a combination of equipment and proper procedure.

Cleaning up spilled enzyme granulates should be done with the use of a vacuum cleaning system fitted with HEPA filtration. The air inflow at the vacuum tool provides some containment of dusts or aerosols at the pickup point. Normal industrial vacuum cleaning systems without HEPA filtration should not be used, as the filtration systems will not adequately remove enzyme dust and/or aerosol before it is returned to the working environment. We refer to **Appendix 2** for the maintenance and testing op equipment utilising HEPA filters.

Liquid enzyme spillages may be washed to a drain by a soft/low pressure water hose. Spill

pans may be drained down to an internal sump, from where it can be pumped directly into a product reclaim system.

Brushes, brooms, compressed air, and high-pressure water **should never** be used for cleaning spillages, as these can either generate significant airborne dust and / or aerosol, or leave behind a wet residue, which can dry out to form a fine dust. Vacuuming followed by wet mopping is preferred.

Depending on the size of a liquid spillage, the use of a sorbent material can be considered. The contaminated sorbent must be shoveled up and placed into a sealed plastic bag / plastic container and disposed of by incineration, or through the wastewater treatment plant [however this will require additional handling controls and disposal of the contaminated packaging]

Respiratory protection should be used for all cleaning / spillage operations because the risk of exposure is always high (see 4.11).

Vacuum cleaners are the preferred tool for cleaning of spillages, plant and equipment. Portable or central vacuum cleaning systems can be used. There are advantages and disadvantages to both systems;

The table in **Appendix 3** describes the options for vacuum cleaning equipment.

Cleaning of Change Parts

In general, the parts cleaning station is an enclosed area where change parts and other equipment are cleaned. It is an isolated room with sufficient exhaust ventilation to maintain a recommended 1m/s face velocity across the door as shown. Change parts should be transported to the cleaning bay/area in a rigid solid sided container to minimise spills. The area should fulfil requirements similar to an isolated discharge area (see 4.7.1) in that it should be under negative pressure with respect to the remainder of the plant.

PPE in accordance with your plant matrix should be worn when inside the room to protect against product splashing back from the wash down. As this is an operation with a high potential for exposure to dust and/or aerosol therefore respiratory protection must be worn as a safeguard (see 4.11).

Cool low-pressure water is used for cleaning whenever possible. The use of hot or high-pressure water should be minimised because they produce high levels of aerosol. Water from parts cleaning runs down the sloped floor of the room and drains to the plant effluent system.

4.11. Personal Protective Equipment (PPE)

4.11.1. Use of Respiratory Protective Equipment (RPE)

In **standard** operational conditions, the use of RPE should always be considered as **secondary** protection where a risk assessment has shown that there is a potential for exposure despite the presence of engineering controls, e.g.

- “On-line” maintenance
- Dealing with small spillages

- Cleaning
- Quality Sampling

RPE should also be used where, due to a failure of a critical engineering control, there is a very significant risk of a peak exposure, e.g. during discharge of enzymes.

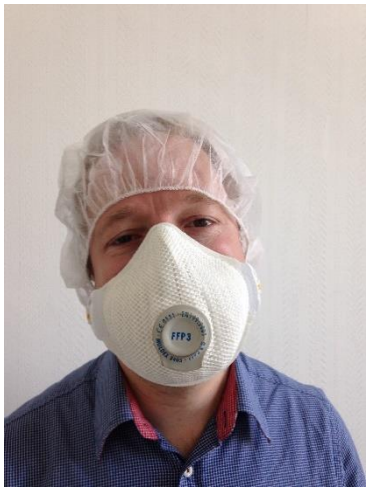
During **trouble-shooting**, RPE may be required as **primary** protection. In this instance, the standard of RPE should be identified by a risk assessment for the task, including the likely level of exposure. Abnormal situations include:

- Major spillage of enzyme raw material
- Dealing with, and repair of, damaged enzyme supply units
- Gross failure of containment or control
- Maintenance or repair of contaminated plant and equipment
- Decontamination of plant and equipment

4.11.2. Standards of Respiratory Protection

The selection of suitable RPE will depend upon the task, the potential level of exposure, and whether the RPE is required for primary or secondary protection. The time for which RPE needs to be worn should also be taken into consideration as should comfort, fit, and compatibility with other PPE, to ensure that there are no issues that could result in incorrect use, or misuse.
The respirator selected must have an assigned protection factor (APF) adequate for the particular workplace exposure.
Divide the air contaminant concentration by the occupational exposure limit (OEL or DMEL) to obtain a hazard ratio. Then select a respirator with an APF greater than or equal to that hazard ratio. It is recommended to comply with the relevant EN standards for RPE (see e.g. EN 529:2005 for APF of different respirator types and according to different countries).
It's highly recommended to conduct a fit testing prior to the use.

The following are examples of the type of RPE available that is often used in pulp & paper mills, to cover a range of contingencies.



Disposable respirators (P1, P2, P3) ***(courtesy: DuPont Nutrition and Biosciences)***

Half-face reusable respirator ***(courtesy: DuPont Nutrition and Biosciences)***

Powered Air Purifying Respirator (PAPR*),* ***(courtesy: DuPont Nutrition and Biosciences)***

The efficiency that is required to provide the necessary protection should be determined by undertaking a risk assessment for the particular task. The recommended minimum standard of respiratory protection is provided below.

For primary protection during **trouble-shooting** conditions, a higher grade of RPE will be required. The minimum standard in this instance should be P3 for airborne dust only and P3SL for airborne aerosol. Again, this should be confirmed by risk assessment. If it is identified that greater protection is required, or because of the duration of the task, comfort may be an issue, then positive pressure respiratory protection should be used.

All employees required to use respiratory protective equipment must be adequately trained in its selection, use and maintenance. The site doctor should assess them as medically fit to wear and use respiratory protection.

In the event normal orinasal face masks cannot be used because the employee has significant facial hair, e.g. a beard, large moustache, etc., and a good face seal cannot be

achieved against the skin, then positive pressure respiratory protection should be used. RPE should be compatible with any other protective equipment provided, such as safety glasses, safety goggles, hearing protection, etc.

4.11.3. Other Personal Protective Equipment (PPE)

In general, skin and eye contact with enzymes, or enzyme products should be avoided through the use of suitable PPE. Proteases may irritate skin, please follow product safety data sheets.

4.11.3.1. Protective Clothing

Under **standard** operational conditions, all employees, contractors and visitors should use the relevant personal protective equipment and work clothing appropriate for the areas they visit or for the tasks they undertake. Often this will be mandated by site policy.

For handling liquid products, the contact surfaces of gloves should be impermeable.

Safety shoes, whilst not related to enzyme safety, should also be used by all persons on site as is appropriate; wellingtons [with safety caps] may be required for major wet cleaning operations.

Decontamination facilities [showers] and a change of protective clothing / work clothing should be available for employees in the event that personal contamination occurs.

Under **emergency** conditions, such as a major spillage, the personal protective equipment should be identified from a risk assessment for each task.

Normal work clothing should be changed / laundered as per site policy, and contaminated work clothing should be changed as soon as is possible depending upon the degree of contamination, and in accordance with the following guidance for personal decontamination. In addition, contaminated work clothing must not be worn in areas such as in offices, meeting rooms, control rooms, canteen, etc. as this presents a risk of exposure outside of the manufacturing / process area. For maintenance or high-risk tasks, where personal contamination is likely, a disposable work wear is an option.

4.11.3.2. Personal Decontamination

Ideally, the plant layout should allow the most convenient and shortest distance from potential exposure areas to personal decontamination facilities. Showers should be available for personal decontamination at the end of shift, after undertaking abnormal tasks, or in the event of an emergency.

Documented procedures should be available for undertaking personal decontamination after undertaking abnormal tasks where the potential for personal contamination is high.

Following high-risk tasks, contaminated clothing should be removed whilst still wearing respiratory protection. Clothing should be placed into a plastic bag for disposal or laundering.

Following decontamination clean work clothing should be available for use.

Chapter 4 - Appendix 1: The Downflow Booth

The downflow booth is designed to provide the best practicable operating environment for handling hazardous materials, affording maximum protection to operators. The booths can be designed in a variety of sizes and shapes depending on the nature of the operation. Low turbulence (laminar) displacement air is supplied vertically from the ceiling plenum. This sweeps down over the operational area ensuring maximum dilution and removal of airborne dust and/or aerosol. To ensure operator safety an average vertical air velocity of 0.45m/s is required. It also ensures that the dust or aerosol that enters the operator's breathing zone is minimised, as long as the operators' head is above the source of contamination. The booth is maintained under slightly negative pressure to the surrounding area ensuring full containment of materials. The negative pressure creates a 10% influx of air into the booth at floor level to "sweep" air contaminated with dust and/or aerosol into the filtration system. Turbulence from draughts across the open face of the booth is minimised by extending the side panels beyond the safe working limit of the unit. This limit is clearly marked on the inside of the walls.

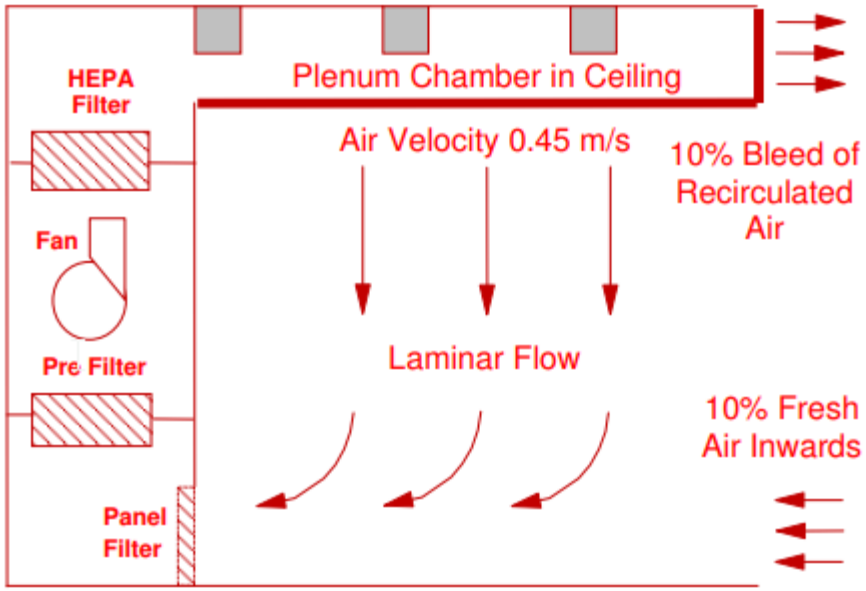


Figure: The Laminar Downflow Booth

Extracted air is treated via a three-stage filtration system before being recycled to the working environment:

Stage One: Panel Filter Class G 4 (replace approx. every 8 weeks)
Stage Two: Pre-filter Class F 8 (replace approx. 1 per year)
Stage Three: HEPA Filter Class H 14 (replace approx. every 3 years)

Each filtration system is monitored via a static pressure gauge, e.g. a Magnahelic or Photohelic gauge.

Chapter 4 – Appendix 2: Maintenance and testing of equipment utilising HEPA filters

Any equipment used for transferring, or cleaning up, of enzymatic materials should be fitted with a HEPA filter on the final discharge which is rated as filter class H14 (1). It is essential that such equipment functions according to the required specification. HEPA filters can be purchased "off-shelf" from a number of suppliers with a challenge test certificate indicating compliance to a specific filter class. However, damage may occur during storage or transit so they should be inspected before being fitted by the machine supplier or trained company personnel. If there are doubts over the integrity of the filter, it can be challenged in situ by use of a liquid particle test aerosol such as Dispersed Oil Particulate (DOP) paraffin oil or Diethyl-hexyl sebacate (DEHS) or equivalent aerosol (2) prior to being used in the workplace.

Criteria for suitable aerosol substances and the equipment and methodology for challenge testing of HEPA filters is set out in the European Standards EN 1822-1:2019 (1) and EN ISO 29463-2:2018 (2). Additional test criteria for HEPA filters are covered in EN ISO 29463-3:2018 to EN ISO 29463-4:2018 and EN ISO 29463-5:2018 (3-5).

Equipment containing a HEPA filter should be place on a scheduled maintenance program. The interval for maintenance should be determined by robustness of equipment, usage of equipment, etc. Equipment should be checked for physical damage (e.g. seals intact, no cracks in internal housing, no loose screws etc.) and, if deemed necessary, the filter performance should be tested in situ.

References

(1) EN 1822-1:2019 – High Efficiency Air filters (EPA, HEPA and ULPA) – Part 1: Classification, performance testing, marking

(2) EN ISO 29463-2:2018 –High Efficiency Air Filters (EPA, HEPA and ULPA) – Part 2: Aerosol production measuring equipment, particle counting statistics

(3) EN ISO 29463-3:2018– High Efficiency Air Filter (EPA, HEPA and ULPA) – Part 3: Testing flat sheet filter media

(4) EN ISO 29463-4:2018 – High Efficiency Air Filters (EPA, HEPA and ULPA) – Part 4: Determining leakage of filter element (scan method)

(5) EN ISO 29463-5:2018 – High Efficiency Particulate Air Filters (EPA, HEPA and ULPA) – Part 5: Determining the efficiency of filter element

https://standards.cen.eu/dyn/www/f?p=204:110:0::::FSP_PROJECT,FSP_ORG_ID:63578,6176&cs=1F88D045A35841F882D0F61F2C2C7A13A

Chapter 4 – Appendix 3: Options for vacuum cleaning equipment

Description	Advantages	Disadvantages
Central Vacuum Cleaning (CVC) systems • Multiple simultaneous users possible • 7.5 meter hoses + tools • Metal tubing network with multiple branches, each with multiple hose connections, to serve defined use zones over a large process area • High vacuum exhauster and filter / receiver to collect waste and fill dust controlledcontainer • Dry clean-up only	• Convenient plug in valves around area at known spill locations • High reliability, with system maintenance, to encourage operators to clean up spills promptly • Minimum equipment (hose/tool) to transport to clean-up site • Emptying waste container can be centrally controlled • Lowest frequency and magnitude of exposures from emptying collected waste at a central, off-line location • Single system to manage versus multiple units	• CVC malfunction affects entire system • Highest initial capital investment • Operators must be trained to purge pipework for long enough to get the waste all the way to the filter/receiver to minimise tubing plugging • Ownership by department or group, not by an individual user • High energy consumption since it runs continuously when process is running • Low efficiency with high / excessive number of users • Long hoses difficult to handle, easy to damage
Portable Vacuum Cleaner (PVC) • One user per PVC • May increase capacity by use of a 200 L metal interceptor drum [on wheels] with attached hose & tools • Exhaust blower with HEPA rated filter • Versions available that are suitable for Liquids handling	• Simple to operate • Low capital investment per unit • Malfunction affects only one unit • Mobile, can relocate to other process areas • Can assign clear ownership to an individual / location • Energy efficient – on only when needed • Shorter hoses are lightweight • Shorter hoses are less likely to be damaged	• Multiple units required to cover entire process area • Although manoeuvrable, ergo-nomically heavy unit (hose, tank, exhauster) to transport to clean-up site if required to be lifted) • Emptying 200 L drum risks major dust exposure and ergonomic effort to operator • Location for emptying must be managed or risk major dust exposures to adjacent people – takes time to roll PVC to off-line area which inhibits timely emptying for next user • Significant maintenance effort is required for PVCs; not designed for continuous service like CVC
Mini CVCs (combination of PVC and CVC concepts) • 2 to 4 simultaneous users per system • Limited tubing network with hose inlets for small area within larger process area • Medium vacuum exhauster and filter / receiver to collect waste and fill removable container • Dry clean-up only	• Low ergonomic effort with minimum equipment (hose/tool) transport to clean-up site • Emptying waste container can be in off- line area Medium frequency and magnitude of exposures from emptying collected waste at an off-line location Malfunction only affects part of operating area • Clear ownership can be assigned	• Medium capital investment - several units can serve process/packing areas • Maintenance effort for multiple equipment systems required • Manual emptying of dust from unit has higher risk of dust exposure and ergonomic effort than CVC but less than PVC • Medium energy- consumption with lower vacuum requirement than CVC runs when process area is running

Chapter 5. Occupational Exposure Assessment & Health Surveillance

5.1 Air monitoring

Introduction:

The HRA for every workplace where enzymes are handled, which must be carried out under the CAD, should incorporate occupational exposure measurements. Due to the extremely low exposure limit values that have been derived for enzymes (see Chapter 2, Appendix 2), other exposure estimation approaches, such as computational models or read-across, are largely not applicable to enzymes. Various sampling protocols, which will be discussed further, provide advice on how to develop an air monitoring strategy for chemical agents. Please contact your enzyme supplier for further guidance on this.

The objectives behind monitoring of airborne enzyme aerosol are clear:

- It enables the quantification of employee exposures
- It enables the overall evaluation of the effectiveness of control measures.
- The results can be used to identify where control measures are found to be insufficient so that they can be improved or workers can be advised to wear RPE.
- The results may also be used to identify where working practices may need to be reviewed in order to reduce exposure; i.e. less prone to create airborne exposure.

Monitoring should be prioritised based on the risk of exposure to enzymes. As basis for the sampling strategy of workplace air the **EN689 standard** can be used, although other standards and guidance documents exist as well (see below). A qualitative assessment of the risks should be first conducted to define the ultimate air monitoring strategy for the site. The strategy may also depend on the outcome of medical surveillance: for example, if immunological testing reveals that there is an increasing trend in the incidence of sensitisation. Moreover, the strategy will also depend on the outcomes of performance assessments of the equipment, work practices and behaviours of the workforce.

Routine air sampling is a quantitative tool to measure levels of background exposure to enzymes and dust; whereas peak sampling is used to measure tasks with high exposures, such as:

- Dispensing
- Weighing
- Mixing
- Material transfers, including sampling
- Handling of empty enzyme supply containers/bags
- Cleaning of plant and machinery
- Technical maintenance
- Any other activities of concern that are indicated by historical results of medical surveillance or air monitoring

Air monitoring includes area and personal sampling and can be undertaken with either high or low volume samplers depending on the analytical restrictions of the type of monitoring to be undertaken. Areas with the highest potential for exposure should be chosen as area sampling locations (such as **material transfer, pulping, wet end, and dry end**). Appropriate monitoring locations can be selected in each facility by an appropriately qualified team, including industrial hygiene and manufacturing personnel.

Both **high** (up to 600 l/min) and **low to medium flow** (2-30 l/min) **samplers** can be used.
Your enzyme supplier can be contacted for advice on measuring inhalable enzyme dust or aerosol.

Different sampling approaches may be used; although it may be necessary to follow local authority regulations or the guidance of EN standards (EN 689:2018 and EN 482:2015, Council Directive 98/24/EC (07/04/1998, amended 05/03/2014); ECHA Guidance, Part R.14, version 3: “Occupational Exposure Assessment”).

EN482 and EN689 are the basic standards for workplace exposure measurements, which recommend that all measurements carried out to compare with limit values should be done within the workers breathing zone. This is, however, not always possible for enzymes. Enzyme monitoring often needs a specific approach; higher flow samplers may be needed due to the low limit of detection (LOD) of the analytical method, but they cannot be used for personal sampling. If the activity is short in duration or has significant opportunity for intermittent peak exposures, the use of a low flow pump to take personal breathing zone samples may not be the best option.

Case study for the pulp & paper industry

Industrial hygiene monitoring has been carried out at paper mills where enzyme products were dosed to the wet end of the papermaking process at manufacturer recommended rates. Enzyme dosing is based on the minimum level needed to achieve the intended technical effects in the process. As part of this assessment, ELISA testing techniques were used to measure employee’s exposure at well-controlled manufacturing sites to potential airborne enzymes during the manufacturing processes, including material transfer, pulping, wet end, and dry end. ***Measured airborne concentrations were less than 40 ng/m3.*** *While air monitoring results may be site-specific, results from mills that have been monitored have shown that potential exposures can be managed with* ***best practices such as introducing enzymes below water line in pulpers, providing adequate exhaust ventilation, preventing and immediately containing spills and leaks, use proper PPE (especially during non-routine activities), and controlling dusting at converting operations.***

Very important is the **calibration** of the sampling equipment; a typical set-up is shown in the picture below.

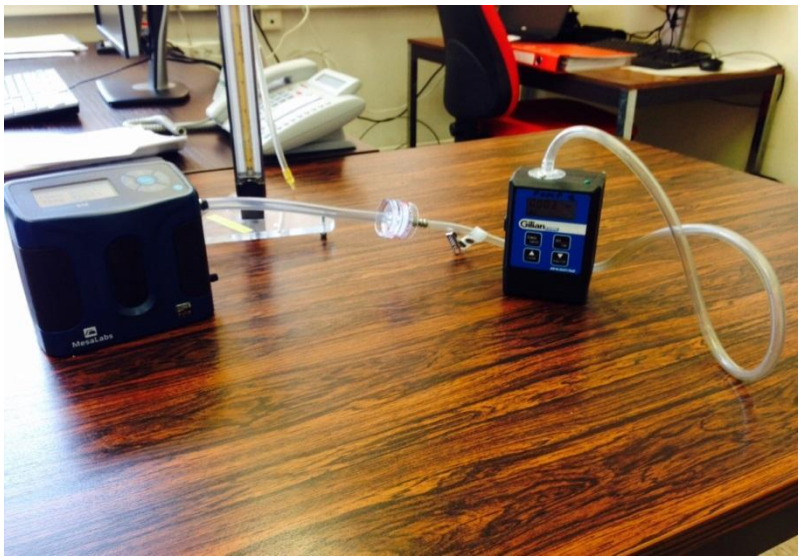


Figure: Calibration set-up for air sampling equipment. *(Courtesy: DuPont Nutrition and Biosciences)*

If there is a national limit value for workers exposure, data interpretation should be done according EN689. Data interpretation should also be done in a similar manner for enzymes for which only a DMEL has been derived.
Data interpretation is perhaps the most difficult part of the whole exposure assessment and depends on the eventual use of the data, e.g.:
- Is this data going to be used to verify the effectiveness of engineering controls and the potential capital investment for the improvement of engineering controls?
- Is this data going to be used to assess the necessary respiratory protective equipment requirements?

Remedial steps should be taken immediately to resolve any exposure conditions leading to an air sampling result above the limit value (OEL and/or DMEL[11]). When re-sampling confirms the high level, then the use of RPE or stopping production should be considered until appropriate controls can be implemented. The follow-up procedure is defined in EN689.
If the exposure in an area is above the limit value, employees should be informed immediately and requested to wear RPE until remedial actions have been implemented and validated.

One aspect of the exposure monitoring is the sampling, but the **analytical part** is equally important. There are two common methods, of which the **activity-based assay** is still the most practical one. The other method is an immunoassay, like **ELISA.** Please contact your enzyme supplier for further guidance on the analytical methods.

Air sampling results, together with the outcomes of the medical surveillance programme, provide valuable information regarding the effectiveness of control measures. However, it is necessary to take into account the limitations of any exposure-monitoring program, e.g.:

- No 'real-time' monitoring equipment available currently. This is only available for particles.
- Monitoring results that are less than the limit value do not guarantee zero incidences of sensitisation.

The nature of the sampling regime means that results are always viewed in hindsight so that it might be difficult to trace back to what went wrong at the time of the sampling. Observations according EN689 should give information during sampling.

In cases where there may be a lack of available qualified internal resources, a certified consultant (industrial hygienist) should be contracted to conduct the air monitoring; and a certified laboratory employed to carry out the air monitoring analysis.

For the components of an air-monitoring program, please consult the "*Guidelines for the safe handling of enzymes in detergent manufacturing"*. Please find the link hereunder: https://www.aise.eu/documents/document/20180405111438-aise-enzymes_safe_handling-v2-2-march_2018.pdf

5.2 Health surveillance

This section is intended to guide occupational health professionals in implementing the current best practice for the health surveillance of workers at risk of exposure to **enzymes.** The protocols recommended in this document may be refined by occupational health specialists based on historical results obtained from their specific area of the Paper & Pulp industry.

[11] https://ec.europa.eu/social/BlobServlet?docId=15614&langId=en

The content of this section is based on the “Current Best Practice for the Health Surveillance of Enzyme Workers in the Soap and Detergent Industry”, issued in March 2001 by the Medical Sub-Committee of the UK Soap and Detergent Industry Association (SDIA). It also includes, with the exception of some modifications, recommendations given in that publication.

It should be emphasised that enzymes generally have a low order of toxicity. There are only two relevant toxicological end points:

- **Respiratory allergy** which is an intrinsic hazard for all enzymes, and
- **Skin irritation**, which is an intrinsic property of enzymes belonging to the class of proteases and only relevant for this class of enzymes.

Different enzyme classes are used in the Paper & Pulp sector (See table 1 and chapter 4).
As described previously in this guideline, enzymes are proteins and, like other proteins, may act as respiratory sensitisers if individuals are repeatedly exposed to airborne aerosols that contains them. Such sensitisation may ultimately lead to respiratory allergy, but it is important to note that not all individuals who become sensitised to enzymes develop symptoms. Therefore, the aim of health surveillance will be to identify those workers who become sensitised and to prevent that such sensitised workers develops allergy symptoms.

Health surveillance is the periodic medical examination of workers potentially exposed to enzymes.

Health surveillance is recommended for employees that are exposed to enzymes in the Paper & Pulp industry. In some countries, employers may be obliged to provide occupational health service if there is a known risk of identifiable disease.

The objectives of health surveillance related to enzyme exposure include:

- Protecting the health of individual employees by the earliest possible detection of any adverse effect, which may be attributed to enzyme exposure.
- Assisting in the evaluation of measures taken to control enzyme exposure.
- Collecting and maintaining objective data to detect and evaluate hazards to health
- Giving guidance on how to continue working in an environment where enzyme exposure cannot be avoided based on the outcome of medical assessments.

Respiratory allergy, which is also called Type 1 allergy, is the only sort of allergy caused by enzyme exposure. Enzymes do not cause allergy via skin contact and, to date, enzymes have not been associated with food allergy.

It is essential to understand that developing a respiratory allergy is a **two-stage process**.

The induction (sensitisation) stage: It begins with the individual being exposed to airborne allergens in the form of dust or wet aerosols. If this exposure is sufficiently high, and lasts for a sufficiently long period, the individual may become sensitised.
The elicitation stage: A sensitised person does not show any allergy symptoms, but the immune system has been activated and specific IgE antibodies have been generated. The presence of specific IgE antibodies can be detected by a skin test or a RAST analysis of the blood. If a sensitised person is

repeatedly exposed at sufficiently high level and for sufficiently long periods, allergy symptoms may develop, and the person is now allergic.

The difference between being sensitised and being allergic is determined by the appearance of allergic symptoms. A sensitised person has no symptoms and sensitisation by itself is not a disease, whereas an allergic person will always present allergic symptoms when exposed to the allergen in question. Sensitisation is the early warning that an allergy may develop. However, prompt and correct intervention may prevent the development of a fully blown allergy.
In the case of enzyme allergy, recent literature suggests that the exposure level required for ***elicitation*** of an allergy is higher than the exposure level required for ***inducing*** sensitisation. Therefore, it is of key importance to prevent peak exposures.

If a person develops an enzyme allergy, it will be a workplace related allergy, and symptoms may develop during or after working hours. In most cases, the symptoms will disappear when the exposure ceases, for example at weekends or during vacations. Symptoms are identical to those presented by allergies towards common allergens. In order of appearance and increasing severity these are:

- itching and redness of the mucous membranes
- watery eyes/nose
- sneezing
- hay fever
- hoarseness or shortness of breath
- coughing
- tightness of the chest
- asthma

The first symptoms to appear will usually be less severe, such as watery eyes or sneezing. If the individual is continually exposed to the allergen for a long period, more and more severe symptoms may appear, and in some cases, these may become chronic.
It is, therefore vital that swift and appropriate intervention should take place as soon as possible; preferably, before any further symptoms appear.

Some people are defined as being ***"atopic",*** which means that they are allergic to one or more of the common allergens like pollen and house dust mites. It has been long discussed whether atopic individuals are at a higher risk of developing allergy, but there is no clarity on this point. Smoking has been identified as a factor, which can increase the risk of becoming sensitised and of developing symptoms.

Some enzymes may cause **skin irritation**. These enzymes all belong to the class of proteases, which degrade protein. No other class of enzymes possesses this characteristic.
The irritation will appear as redness of the skin, and only after intensive contact. The irritation will be localised and disappears after the skin contact with the protease enzyme has ceased.
Skin irritation should not be mistaken for a skin allergy, as enzymes do not cause skin allergies.

An enzyme allergy is exclusively an occupational health hazard for people working in the enzyme manufacturing industry; or for downstream users such as workers handling enzymes as raw materials in the Paper & Pulp industry. Several studies have shown that consumers of products that contain enzymes in today's market are not at risk.

Therefore, an enzyme allergy is the result of an occupational exposure and its cause will always be found in the working environment.

Guidance for a Health Surveillance programme

Elements of such a programme could be:

- **A pre-employment testing**
- **Medical history** could be assessed with particular reference to, for example, asthma, allergic rhinitis, eczema, urticaria, allergies, chronic lung disease and any medication.
- **A respiratory questionnaire** could be completed including details of smoking habits. Examples of such pre-employment and periodical questionnaires are given in the *"AISE Guidelines for the Safe Handling of Enzymes in Detergent Manufacturing*"[12]
- **Assessment of lung function** could be made using a suitable spirometer and following an accepted standardised procedure and protocol in order to minimise measurement errors. The parameters that could be measured are FEV1, FVC, and PEFR.
- **Immunological Tests,** e.g. **skin prick** or **serological tests** could be performed. The purpose of immunological monitoring is to monitor the appearance of sensitisation among the workforce, revealed by the development of specific IgE antibodies. It is important to remember that sensitisation is not a disease: it is an indication that a person has been exposed, and may be on their way to developing an allergy.

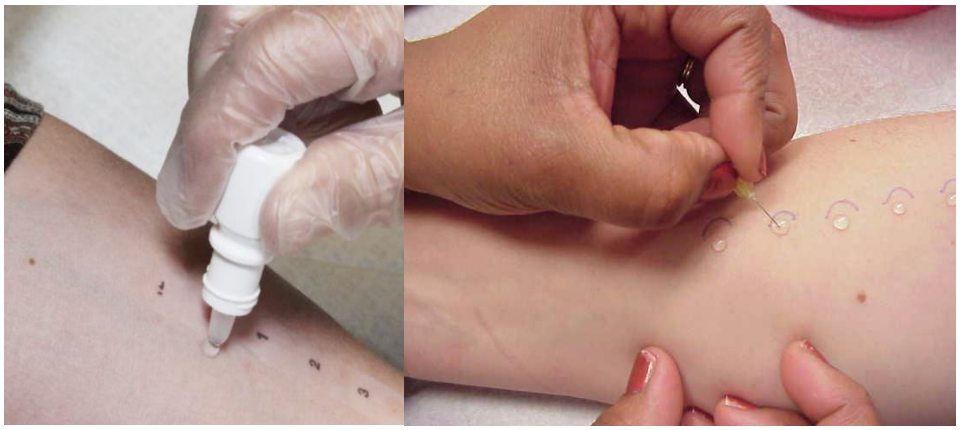


Figure: Skin prick testing

Those with **normal findings** may continue to work until the next examination.

Those who have developed a **positive immunological test** result to enzyme and have no other adverse findings may continue to work with enzymes, although an increased frequency of medical surveillance of such workers may be appropriate.

Those with **abnormal findings** to the respiratory questionnaire, which (in the opinion of an occupational health professional) could be due to enzymes; and those with impaired lung function according to spirometry readings; should have immediate further assessment.

Those who show a **continuing downward trend in lung function** should be carefully assessed regarding the need to remove them from further work with enzymes.

References

1. Basketter, D. A., Kruszewski, F. H., Mathieu, S., Kirchner, D. B., Panepinto, A., Fieldsend, M., ... & Concoby, B. (2015). Managing the risk of occupational allergy in the enzyme detergent industry. *Journal of occupational and environmental hygiene*, 12(7), 431-437.

[12] AISE: Guidelines for the safe handling of enzymes in detergent manufacturing (version 2.2, 2018): https://www.aise.eu/documents/document/20180405111438-aise-enzymes_safe_handling-v2-2-march_2018.pdf

Useful links - Example of general information on health surveillance (UK example) http://www.hse.gov.uk/coshh/basics/surveillance.htm

Chapter 6. Concluding Remarks & Acknowledgements

In this document, the authors have demonstrated the importance of controlling aerosol exposure throughout the supply chain of the pulp & paper industry. This control is achieved based on a holistic approach: from a technical perspective in the form of equipment and processes, through operator behaviours and effective management. The advice and best practices provided in this document should be read in conjunction with local guidelines and current regulations where applicable.

Should you require further guidance on enzyme safety you are recommended to contact your enzyme supplier.

This document will be updated as new and significant insights become available.

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