[Possibility for MSCA Logo]

Analysis of the most appropriate risk management option (RMOA)

Substance Name: **Amylase, α-**

EC Number: **232-565-6**

CAS Number: **9000-90-2**

Authority: **United Kingdom**

Date: **March 2018**

Cover Note

Amylase, α- (AA), is a respiratory sensitiser. It was added to the CoRAP (Community Rolling Action Plan) in 2013 to clarify concerns about the potential exposure of workers and consumers. The evaluation was concluded in March 2016. Information obtained during the course of the evaluation raised a concern that hazard and safe use information may not always be communicated effectively to end users. The evaluation also identified a possible concern if enzymes are added to hand dishwashing liquids supplied to consumers and these liquids are then used for activities outside the scope of the exposure scenario. During the preparation of this RMOA, new information was been obtained and the registrants have updated the exposure scenarios for industrial use as a processing aid and consumer use in hand dishwashing liquids. Also new guidance aimed at workers is being developed to help communicate messages about safe use. In the light of this, no further regulatory action is necessary at this time. Given that the range of uses for AA could expand in the future, it is important that all registrants maintain active communications with downstream users to ensure that the risks from all foreseeable workplace and consumer uses are properly assessed.

Although this RMOA focusses on AA, the conclusions may be relevant to other enzymes.

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1 IDENTITY OF THE SUBSTANCE

Amylase, α- (AA) is an enzyme. Enzymes of the amylase class catalyse the hydrolysis of α-1-4 glucosidic linkages of polysaccharides such as starch, glycogen or their degradation products. AA attacks sub terminal and internal 1:4 links in the starch molecule to break the long chains into small fragments. AA enzymes are derived from a variety of organisms and represent a diverse group of substances whose molecular weights vary from 10000 to 140000 but which share the same enzymatic activity. Enzymes from different organisms express optimum enzymatic activity under different conditions and this determines the uses to which enzymes are put. Commercial AA enzymes are usually derived from either bacterial or fungal sources. AA derived from bacterial sources tends to be preferred for manufacture of detergents and textile processing.

Identity information for the AA enzymes covered in the substance evaluation performed by the UK REACH Competent Authority in 2015 is provided in table 1. This Risk Management Options Analysis (RMOA) specifically examines options to address the concerns that were identified during the substance evaluation for the AA enzymes covered in the substance evaluation. Although this RMOA focusses on AA covered by CAS number 9000-90-2, the conclusions may be relevant for other enzymes.

1.1 Other identifiers of the substance

Table 1: Other Substance identifiers

Public name:	Amylase, α-
EC number:	232-565-6
CAS number:	9000-90-2
Index number in Annex VI of the CLP Regulation:	647-015-00-4
IUBMB Name	Alpha amylase
Enzyme class number	3.2.1.1
Systematic name	4-alpha-D-glucan glucanohydrolase
Other Constituents	The enzyme is produced by organisms which meet the criteria for “Safe Strain Lineage Concept" in "Safety evaluation of technical enzyme products with regards to the REACH legislation" dated March 25, 2009, published by Enzyme REACH Consortium (http://www.enzymes-reach.org/). Constituents deriving from the fermentation or extraction process include: carbohydrates, inorganic salts, lipids and other proteins + peptides and amino acids.

Type of substance ☐ Mono-constituent ☐ Multi-constituent ☒ UVCB

Structural formula:

Not available

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table 2: Completed or ongoing processes

RMOA		☐ Risk Management Option Analysis (RMOA) other than this RMOA
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☒ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restri -ction	☐ Annex XVII
Harmonised C&L		☒ Annex VI (CLP) (see section 3.1)
Processes under other EU legislation		☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009
		☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments
Previous legislation		☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
		☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)
(UNEP) Stockholm convention (POPs Protocol)		☐ Assessment
		☐ In relevant Annex

Other processes/ EU legislation	☒ Other (provide further details below)

AA (and other enzymes) has applications in a wide range of sectors and consequently a complex legislative framework is evolving. Since this RMOA targets uses that were covered in the REACH substance evaluation for AA, the only legislation that will be discussed here is that which is relevant to these uses (i.e. worker protection legislation, consumer protection legislation and relevant product specific legislation). Specific provisions for enzymes including AA are also included in legislation relating to animal feed additives, cosmetics, pharmaceuticals and food safety. These provisions usually apply to enzymes as a generic group rather than individual enzymes. Further information on these additional uses can be found in an old document prepared for the European Commission (EU, 2002).

Worker protection:
Chemical Agents Directive (98/24/EC)[1]

The Chemical Agents Directive (CAD) 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 a hazardous chemical agent if it:

- meets the criteria for classification as hazardous within any physical and/or health hazard classes laid down in Regulation (EC) No 1272/2008 of the European Parliament and of the Council[2], whether or not that chemical agent is classified under that Regulation, or

- which, whilst not meeting the criteria for classification as hazardous in accordance with the above may, because of its physico-chemical, chemical or toxicological properties and the way it is used or is present in the workplace, present a risk to the safety and health of workers.

Since AA has a harmonised classification as Resp. Sens. 1, it meets these criteria. There are no specific provisions for AA or enzymes as a generic class of substances in CAD therefore AA is 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. In particular, risk assessments must be updated if there have been significant changes or if the results of health surveillance show it to be necessary. The employer must take the necessary preventive measures to eliminate or reduce to a minimum the risks identified in

[1] 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)

[2] 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).

the risk assessment following a hierarchy of prevention measures. The hierarchy (described in Article 6) identifies elimination and substitution as the preferred approach to manage risks. Where this is not possible the following shall be considered in order of priority:

a) design of appropriate work processes and engineering controls and use of adequate equipment and materials, so as to avoid or minimise the release of hazardous chemical agents which may present a risk to workers' safety and health at the place of work;

b) application of collective protection measures at the source of the risk, such as adequate ventilation and appropriate organizational measures;

c) where exposure cannot be prevented by other means, application of individual protection measures including personal protective equipment.

This is supported by the general principles for the prevention of risks associated with hazardous chemical agents which are described in Article 5. This article says risks to the health and safety of workers at work involving hazardous chemical agents shall be eliminated or reduced to a minimum by:

a) the design and organisation of systems of work at the workplace,

b) the provision of suitable equipment for work with chemical agents and maintenance procedures which ensure the health and safety of workers at work,

c) reducing to a minimum the number of workers exposed or likely to be exposed,

d) reducing to a minimum the duration and intensity of exposure,

e) appropriate hygiene measures,

f) reducing the quantity of chemical agents present at the workplace to the minimum required for the type of work concerned,

g) suitable working procedures including arrangements for the safe handling, storage and transport within the workplace of hazardous chemical agents and waste containing such chemical agents.

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 European Union (EU) that are fully complying with national workplace legislation should be managing the risks from AA and AA-containing products according to these principles.

Consumer protection:
General Product Safety Directive (2001/95/EC)[3]

The General Product Safety Directive (GPSD) aims to set minimum standards for the safety of products supplied to the EU market. It contains the general

[3] Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety (Text with EEA relevance)

requirement that producers shall be obliged to place only safe products on the market. In this context, the terms product and safe product are defined in the following way:

a) ‘product’ shall mean any product — including in the context of providing a service — which is intended for consumers or likely, under reasonably foreseeable conditions, to be used by consumers even if not intended for them, and is supplied or made available, whether for consideration or not, in the course of a commercial activity, and whether new, used or reconditioned.

b) ‘safe product’ shall mean any product which, under normal or reasonably foreseeable conditions of use including duration and, where applicable, putting into service, installation and maintenance requirements, does not present any risk or only the minimum risks compatible with the product's use, considered to be acceptable and consistent with a high level of protection for the safety and health of persons, taking into account the following points in particular:
    (i) the characteristics of the product, including its composition, packaging, instructions for assembly and, where applicable, for installation and maintenance;
    (ii) the effect on other products, where it is reasonably foreseeable that it will be used with other products;
    (iii) the presentation of the product, the labelling, any warnings and instructions for its use and disposal and any other indication or information regarding the product;
    (iv) the categories of consumers at risk when using the product, in particular children and the elderly.

The broad definition of “product” means that AA containing mixtures that are available for use by consumers fall within the scope of this directive. The directive states that a product is deemed safe once it conforms to the safety provisions provided in European legislation or national legislation of MS adopted in accordance with EU law. Demonstration of safe use in the context of a REACH registration is likely to be taken as evidence that a product can be regarded as safe under the GPSD.

Work is ongoing on a product safety and market surveillance package which aims to replace the GPSD with a new Regulation[4]. The proposed new Regulation will retain the requirement that all consumer products must be safe when placed or made available on the EU market and supplements this with an obligation on manufacturers to establish a technical documentation regarding their products which shall contain the necessary information to prove that their product is safe.

The proposal includes a revised definition for the term ‘safe product’. For the purposes of the proposed Regulation ‘safe product’ means any product which, under normal or reasonably foreseeable conditions of use of the product concerned, including the duration of use and, where applicable, its putting into service, installation and maintenance requirements, does not present any risk or only the minimum risks compatible with the product's use, considered acceptable and consistent with a high level of protection of health and safety of persons. Products containing enzymes including AA will fall within the scope of the proposed new Regulation.

[4] http://eur-lex.europa.eu/procedure/EN/2013_49 (accessed 19 September 2017)

Product specific legislation:
The Detergents Regulation (EC) No 648/2004[5]

This Regulation establishes rules designed to achieve the free movement of detergents and surfactants for detergents in the internal market while, at the same time, ensuring a high degree of protection of the environment and human health. For the purpose of this Regulation:

'Detergent' means any substance or mixture containing soaps and/or other surfactants intended for washing and cleaning processes. Detergents may be in any form (liquid, powder, paste, bar, cake, moulded piece, shape, etc.) and marketed for or used in household, or institutional or industrial purposes.

Other products to be considered as detergents are:

a) 'Auxiliary washing mixture', intended for soaking (pre-washing), rinsing or bleaching clothes, household linen, etc.;
b) 'Laundry fabric-softener', intended to modify the feel of fabrics in processes which are to complement the washing of fabrics;
c) 'Cleaning mixture', intended for domestic all purposes cleaners and/or other cleaning of surfaces (e.g.: materials, products, machinery, mechanical appliances, means of transport and associated equipment, instruments, apparatus, etc.);
d) 'Other cleaning and washing mixtures', intended for any other washing and cleaning processes.

'Washing' means the cleaning of laundry, fabrics, dishes and other hard surfaces.

'Cleaning' means the process by which an undesirable deposit is dislodged from a substrate or from within a substrate and brought into a state of solution or dispersion.

In relation to enzymes including AA, the Regulation includes a requirement that all detergent products containing enzymes sold to the general public should list this constituent on the label irrespective of the concentration present in the product (see Article 11(3) and Annex VII A). Typically detergent products will not list the specific enzymes or enzyme activities that are present in the formulation but may use words such as "contains enzymes". Several of the uses identified in REACH registrations for AA cover products that fall within the scope of the Detergents Regulation. During the evaluation, it was clarified that this labelling requirement extends to medical device cleaning products that carry the CE mark:

If the enzymatic mixture is compliant with the definition of detergent and is used as "accessories" ('accessory' is defined in the Medical Devices Directive (93/42/EEC) as an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device) the mixture will be subject to both the Detergents Regulation and the Medical Devices Directive and should be both CE marked and compliant with the labelling requirements of the Detergents Regulation.

It is therefore expected that labels on all detergent products containing AA will alert users to the presence of enzymes in the product. The label cannot provide warnings of a potential sensitization hazard if this contradicts the rules laid out in

[5] Regulation (EC) No 648/2004 of the European Parliament and of the Council of 31 March 2004 on detergents (Text with EEA relevance) (as amended by Commission Regulation 1336/2008)

the CLP Regulation for provision of such information (see section 5.2.1 for further information). However, the label on the detergent product should communicate instructions for use and any special precautions that may need to be communicated for a particular use, if required.

No other legislation has been identified that is relevant to the uses of AA that are covered in REACH registrations.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

Table 3: Harmonised classification

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
647-015-00-4	Amylase, α-	232-565-6	9000-90-2	Resp. Sens. 1	H334		

For more information about the hazard classification of industrial enzymes please see a document prepared by ECHA, June 2016.[6]

3.1.2 Self-classification

- In the registration(s):

See above

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Resp Sens 1	H334	This is applied in 1179 notifications[7]
Acute Tox.3	H301	This is applied in 1 notification[7]
Acute Tox.4	H312	
Skin Corr.1B	H314	
Acute Tox 3	H331	
Resp Sens 1	H334	
Aquatic Acute 1	H400	
Aquatic Chronic 1	H410	
Resp Sens 1A	H334	This is applied in 1 notification[7]

[6] http://www.amfep.org/sites/default/files/hazard%20classification%20of%20enzymes.pdf (accessed on 19 September 2017)

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

Not applicable

3.1.4 CLP Notification Status

Table 4: CLP Notifications

	CLP Notifications[7]
Number of aggregated notifications	6
Total number of notifiers	1181

3.2 Additional hazard information

AA has a harmonised classification under CLP for respiratory sensitization category 1 (Resp Sens 1). Like other enzymes, it is a protein based allergen. The mechanism that underlies allergic reactions to protein-based allergens is a two-stage process. The first stage is induction in which an individual develops a population of allergen specific immunoglobulins (IgE). At this stage, an individual may not notice any change has taken place and they will be able to carry on with their life as normal. However, the presence of allergen specific IgE can be detected using tests such as the skin prick test or a blood test.

The second stage of the process is elicitation when a sensitised individual starts to experience respiratory symptoms. If the respiratory symptoms are specifically caused by substances someone is exposed to at work, a diagnosis of occupational asthma can be made. To prevent the symptoms becoming unmanageable, these people often need to change their jobs to avoid continuing exposure. If they remain with their employer, the employer will need to take steps to prevent the worker being exposed to the agent that is causing the symptoms.

Although substances may have the potential to cause occupational asthma, not everyone who is exposed will develop asthma. It is likely that there is a spectrum of susceptibility across the population. However, our knowledge about the factors that make some individuals more susceptible than others is incomplete. It has been suggested that atopic individuals who suffer from hay-fever or house dust mite allergy may be more susceptible to other protein allergens (Larsen *et al*, 2007; Fishwick *et al*, 2008; Vandenplas, 2011; Green and Beezhold, 2011). Limited understanding about why some develop asthma when others with seemingly similar exposure do not makes it difficult to identify exposure-response relationships and dose-thresholds for asthmagens.

[7] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 19 September 2017)

Since it is not possible to identify thresholds of effect, REACH registrants calculated derived minimum effect levels (DMELs) to enable a quantitative risk characterisation to be performed. They based the long-term worker inhalation DMEL of 60 ng/m^3 on the Ceiling Threshold Limit Value (TLV) for subtilisins established by the American Conference of Governmental Industrial Hygienists (ACGIH) in the early 1970's. This was the lowest level (based on measurements for the protease subtilisin) that could be achieved in the detergents industry at the time. The long-term consumer inhalation DMEL of 15 ng/m^3 is based on a lack of evidence in consumer product trials that products potentially giving exposures of this magnitude cause induction of sensitisation. No other DMELs have been derived.

The evaluation concluded that there is a high degree of uncertainty about the level of risk for induction or elicitation of symptoms at the DMELs which have been adopted by the registrants. The available evidence suggests the risks for induction of sensitisation and the elicitation of upper and lower respiratory symptoms in sensitised individuals may be increased with exposures in the low ng/m^3 range. For example, a reference value of 0.9 ng/m^3 (8-hr TWA) has been identified by the Health Council of the Netherlands as a level of exposure to fungal AA derived from *Aspergillus oryzae* that is associated with an additional 1% risk of induction of sensitisation (Health Council of the Netherlands, 2014)[8]. Alternative DMELs were not proposed during the evaluation (ECHA, 2016). Since the evaluation was completed, no new information has been published that would change this conclusion.

Additional information to inform classification and labelling decisions

Although it is currently not possible to quantify the risk at any given level of exposure, some information is available about the frequency of occurrence of cases. This information is presented here since it is relevant to discussions about possibly reclassifying AA as Resp Sens 1A if this is thought to be a useful risk management measure.

Brandt *et al* (2009) published a nested, matched case-referent analysis using a cohort of workers employed at a detergents manufacturing facility between 1 January 1989 and 31 July 2002. Over this time, 2007 workers were employed. Of these, health and employment records were available for 1697 workers (85%) and 884 had worked for more than 4 months (median length of employment 39 months, interquartile range 13-80 months). A total of 221 employees developed chest disease (incidence rate 3.5 per 100 person-years) and 214 employees developed eye/nose disease (incidence rate 3.3 per 100 person-years). Seventy four percent of cases were identified within the first 4 years of employment.

For this cohort, the risk of chest symptoms and disease (chest tightness, shortness of breath or wheeze, diagnoses of asthma and new use of inhalers) was approximately doubled at an estimated mean exposure intensity of 8 ng/m^3 (odds ratio 1.87, 95% confidence interval (CI) 1.01 to 3.48). For eye/nose disease (new reports of eye/nose symptoms, hay fever, diagnoses of rhinitis and use of nasal medication) a significant increase in risk was apparent with an estimated exposure of 2.3 ng/m^3 or higher (odds ratio 1.80, 95% CI 1.0.1 to 3.22). These

[8] This risk estimate was derived from two studies in bakers. It is not clear if the mixed allergen exposure situation that exists in bakeries might have influenced the exposure/response relationships underpinning this risk estimate. It is also not clear if this risk estimate can be applied to alpha amylases derived from other organisms which are also covered by EC 232-565-6. For these reasons, no recommendations are made in this RMOA to use this reference value in quantitative assessments.

exposure estimates are derived from measurements of airborne protease in static samples (protease was measured as a surrogate for all enzymes including AA that were used on site) and adjusted to reflect potential personal exposure using the possibly inaccurate assumption that the ratio of protease to dust in personal total dust samples will be the same as the ratio observed for static area samples. Further details of the study and the methods used to obtain quantitative exposure estimates are provided in the AA substance evaluation report (ECHA, 2016).

In a study to investigate exposure to enzymes from a prototype personal cleansing bar containing a protease normally used in laundry detergents, it was found that airborne levels of between 5.7 – 11.8 ng/m^3 could be generated during use of the bar in a shower (SDA, 2005). During pilot clinical trials of the product, 4 out of 61 participants developed enzyme specific IgE after 4-6 months use of the product for showering. No further details were reported in the SDA publication. It should be noted that exposures in this case would be via multiple routes (inhalation, mucosal tissue, hydrated skin) and it is not clear which route made the greatest contribution to the antibody reaction.

Information has been published from health surveillance programmes operated by the European detergents industry (Basketter *et al*, 2015). This covers around 20000 - 25000 workers employed at production sites across the EU during the period 2006-2010. Among this group the prevalence of workers with raised enzyme specific IgE was around 8%. The yearly incidence rate for workers testing positive for enzyme specific IgE for the first time is below 1% with clinical symptoms occurring in less than 1 in 10 of workers with enzyme specific IgE, i.e. in less than 0.1% of those working with enzymes. The report did not specify which enzymes were involved in any of these cases. The percentages are comparable to percentages provided informally for enzyme manufacturing. The detergents manufacturing sector aims to keep airborne levels of enzymes below 60 ng/m^3 with some companies working to more stringent enzyme specific standards ranging from 5 – 20 ng/m^3 (Basketter *et al*, 2010).

Prevalence information is also available from a recent study in which blood samples from 813 workers from workplaces using genetically modified enzymes in food, beverage, chemical, detergent and pharmaceutical industries were analysed for enzyme specific IgE (Budnik *et al*, 2016). When blood samples were screened for the presence of enzyme specific IgE against the specific enzymes used at the worker's place of employment, it was found that 44% tested positive for "amylase" (the group covers workers using various forms of AA) with 41% testing positive for stainzyme (an amylase obtained by fermentation of genetically modified organisms). Other enzymes tested for and the percentage of blood samples testing positive for enzyme specific IgE included pancreatinin (35%), savinase (31%), papain (31%), ovozyme (28%), phytase (16%), trypsin (15%) and lipase (4%). The average across all enzymes was 23%.

Symptom questionnaire data was available for a sub-group of 134 of these workers. Of the sub-group, 64% were asymptomatic, 19% had work related rhinitis or conjunctivitis and 17% had work related wheezing and/or asthmatic dyspnoea. The occurrence of symptoms was significantly correlated to the presence of specific IgE antibodies against workplace enzymes. Correlation to atopy status was not recorded. Owing to commercial secrecy restrictions, the authors were not able to link findings to specific bioengineered enzyme formulae and no exposure information was available. The paper reported that the enzymes giving greatest prevalence of sensitisation were mainly used in the wash, clean and home care product industries. These uses are covered in REACH registrations for AA.

Health surveillance data are not available from other sectors but an examination of cases of occupational asthma reported to the THOR (The Health and Occupation Research Network) scheme in the UK between 2005 and 2014

suggests between 16 and 38 cases of occupational asthma reported in this period were due to enzymes. These figures exclude cases in bakers since bakery work is outside the scope of this RMOA. THOR gathers information from specialist physicians, occupational physicians and general practitioners on work-related ill health. Of the reported cases, 11 worked in detergents manufacture, 2 relate to use of endoscope cleaning solutions, 1 worked in the cleaning sector and 2 cases, where the cause was specified as protease, were manufacturing process workers. These last 2 cases were reported by occupational physicians who report for 1 month in the year and hence 2 reported cases could be equivalent to up to 24 potential cases. The pattern of reporting suggests around 1-2 cases arising per year rather than isolated clusters. No information is available on the exposure situations that led to these cases.

The cases reported to THOR represent a small number when compared with the size of the potentially exposed population. The UK National Office of Statistics and Workforce data survey in 2017 [9] identified around 5.5 million employees (male and female, full and part time workers) working in sectors where exposure to industrial enzymes including AA may occur (manufacture of food products, beverages and tobacco have been excluded to target the potentially exposed population to the uses identified in the REACH registration)[10]. It is not known how many are regularly exposed in these occupations and there is no information on the intensity of exposure that may be experienced. It is likely that for the majority of these workers exposure to enzymes occurs infrequently during their working day, or maybe less than daily. Even among workers who use enzyme containing products several times a day, their exposure intensity per use may be low. It is therefore difficult to compare the numbers of cases reported to THOR with the prevalence and incidence rates reported in other sources.

Summary

In summary, the hazardous property giving rise to concern is respiratory sensitisation. So far, no clear evidence is available to identify thresholds of effect. This is in part due to limitations in the methods to quantify exposure, but also due to the fact that our understanding of the process by which individuals become sensitised is limited. In particular, there is uncertainty about the role of transient peak exposure vs background exposure and the factors that make some people more susceptible than others. The quantitative exposure-response information that is available suggests the risks for the induction of enzyme specific IgE and the elicitation of respiratory symptoms may be increased with exposures in the low ng/m^3 range. There is also uncertainty about the prevalence of allergic symptoms in workers and the general population. Although few cases are reported to THOR compared with the size of the potentially exposed population, it is possible that many more cases go unreported and possibly unrecognised if the symptoms that an individual experiences are mild. Given that Budnik *et al* (2016) suggests that a potentially high percentage of workers exposed to enzymes may develop enzyme specific IgE this could suggest an ongoing problem.

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[9] https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/datasets/employeejobsbyindustryjobs03 (site accessed 6 October 2017 – calculations based on June 2017 totals published in Sept 2017)

[10] Includes manufacture of textiles, manufacture of leather and related products, manufacture of paper and paper products, manufacture of basic pharmaceutical products, water collection, treatment and supply, sewerage, food and beverage service activities, scientific research and development, veterinary activities, human health activities, residential care activities, washing and (dry)-cleaning of textile, and fur products.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[11]

4.1 Tonnage and registration status

Table 5: Tonnage and registration status

From ECHA dissemination site	
Registrations	☒ Full registration(s) (Art. 10) ☐ Intermediate registration(s) (Art. 17 and/or 18)
Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported)	1,000-10,000 tpa

There are 5 active registrants listed on ECHA's dissemination site:

- Genencor International B.V. - OR-CN, Archimedesweg 30, 2333 CN Leiden, Netherlands
- Genencor International B.V. - OR-US, Archimedesweg 30, 2333 CN Leiden, Netherlands
- Genencor International BVBA, Komvest 43, 8000 Brugge, Belgium
- Genencor International Oy, Tiilikantie 15, FI-42300, Jämsänkoski, Finland
- Novozymes A/S, Krogshoejvej 36, 2880 Bagsvaerd, Denmark

4.2 Overview of uses

Enzymes including AA are manufactured by a fermentation and recovery process which takes place in predominantly closed systems. Enzymes are not supplied as fine powders but are formulated by registrants into liquids or granulates (minimum particle diameter 300 µm) which typically contain a maximum of 15% active enzyme protein (aep). These liquids and granulates are then used by downstream formulators to produce products which typically contain less than 0.5% aep and in some cases much less. End users may be workers or consumers. They may be supplied with concentrated products which require dilution before use or ready-to-use formulations.

[11] Dissemination site accessed on 4 September 2017.

AA-containing products have applications in a range of sectors where there is a need to break down starch molecules. They are good alternatives to harsh chemicals because they are effective in small quantities and have a very specific action on starch molecules and offer environmental benefits such as lower temperature processing. The recognised advantages over non-enzyme options have resulted in a rapid growth in the market for enzyme-based products (Adrio and Demain, 2014).

For the uses covered in registrations, the largest volumes are used as industrial processing aids and in laundry products supplied to consumers. Smaller volumes are supplied for laundry products intended for professional use. AA is also supplied for use in dishwashing products supplied for consumer and professional use and as a processing aid in the manufacture of pulp and paper products, as a processing aid in the manufacture of textiles, in products to clean medical devices, drain cleaning products and professional floor and hard surface cleaning products.

In laundry products, AA acts to enhance stain removal. In dishwashing and cleaning products including products supplied to clean medical devices, AA enhances the removal of solid contaminants containing starch residues. Stiefel *et al* (2016) reported that enzymes significantly improve endoscope cleaning without damaging this delicate medical equipment. For patient safety, use of these products may be increasing. In textile manufacture AA is used to remove the starch-based 'sizes' that are applied to warp threads to protect them during weaving. They are an effective alternative to desizing agents based on acids, bases or oxidising chemicals because they can bring about complete removal of the size without damaging the fabric. In paper and pulp manufacture, AA is used to treat cellulose pulp, increasing fibre strength.

Table 6 lists the uses for AA that were covered in REACH registrations in 2015.

Table 6: Uses

	Use(s) described in the alpha amylase registration
Uses as intermediate	Not applicable
Formulation	Formulation of alpha amylase Formulation of enzyme containing products at downstream user sites
Uses at industrial sites	Use as processing aid
Uses by professional workers	Processing aid used by professionals Laundry products (I&I laundry) Machine dishwashing products (I&I ware wash) Hand dishwashing products Cleaning of medical devices
Consumer Uses	Consumer cleaning products Laundry and machine dishwashing products Hand dishwashing products
Article service life	Not applicable

4.3 Additional information

4.3.1 Measured exposure data

4.3.1.1 Background information on measuring enzymes in air

The first industrial enzymes to be used commercially were proteases and the first methods to monitor workplace exposure were based on proteolytic substrate assays using total dust samples collected using static sampling devices. Static sampling devices had to be used because of the large volumes of air that needed to be sampled to collect sufficient dust for analysis. Over the years, methods to detect protease in air have been refined and standardised. As other enzymes (including genetically engineered enzymes) have been commercialised, other methods have been developed to measure these other enzymes in air. Although modern enzyme containing products usually contain a mixture of different enzymes, where proteases are included in enzyme mixtures it is usual to measure protease as a surrogate for all enzymes in the product. This allows companies to demonstrate compliance with the occupational exposure limits for subtilisins (a protease) that have been established in national workplace legislation in several countries (see section 4.3.3.1). But this also means that a lot of the exposure data collected during routine workplace air monitoring and published in studies looking at the health of workers exposed to enzymes is expressed in terms of protease levels. It may also have been obtained using static sampling devices because although sufficiently sensitive analytical methods are now available to allow personal monitoring data to be collected, this is not routinely done. This use of static sampling data, rather than personal exposure monitoring, makes it difficult to define quantitative exposure-response relationships for respiratory sensitisation.

A source of uncertainty that needs to be taken into account is whether or not inactive enzymes have any role in the induction of immune sensitisation and elicitation of respiratory allergy and whether inactive enzyme will contribute to the measured levels in air when immunoassay based analytical techniques (e.g. the enzyme linked immunosorbent assay (ELISA)) are used to quantify airborne enzyme levels. The functional substrate assays that detect proteolytic (or other enzyme) activity only quantify active enzyme concentrations. It is therefore not clear which of these analytical methods is measuring the concentration in air which is most relevant for induction and elicitation.

4.3.1.2 Levels of exposure associated with REACH registered uses

The exposure data provided in registrations is based on measured data and includes: high volume static sampling data from registrants' sites; high volume static sampling data from downstream user sites; simulation studies covering professional and consumer uses; a small number of personal monitoring samples covering professional hard surface cleaning and consumer product trial data. Often protease has been measured as a surrogate for AA where enzyme mixtures are present. It is possible to perform analyses for multiple enzymes from the same sampling filters using specific immunoassays or where the enzymes have very different substrate specificities. This has been done in some cases meaning that the measured data set contains some data points for AA in addition to the surrogate protease data. The limits of quantification (LOQ) for these measurement methods typically range from around 0.5 – 3 ng/m^3, but in some cases has risen as high as 8 ng/m^3. This is significant because the exposure response information discussed in section 3.2 suggests levels of exposure in the low ng/m^3 range may potentially carry an increased risk of inducing enzyme specific IgE (sensitisation). This means that any situation in which airborne

enzyme levels are measureable is potentially of concern. Decisions on actions to address this potential concern should take account of the technical risk management measures that are available or could be implemented in addition to the measures that are already in place.

Measureable levels have been reported for manufacturing and formulation at registrants' sites and for formulation at downstream user sites where enzyme concentrates are formulated into products for end users. Where end products containing 0.5% aep or less are used, airborne enzyme levels are generally below the limits of detection. However, situations have been identified where measureable levels were recorded. Details of the measurement methods and limits of detection are available in the substance evaluation report (ECHA, 2016). Since the risk of inducing enzyme specific IgE at the levels measured for REACH registered uses is unknown, a greater emphasis was placed in the substance evaluation on a qualitative assessment of the suitability of the identified operating conditions (OCs) and risk management measures (RMMs) to manage the risks for respiratory sensitisation.

4.3.2 Conclusions from the substance evaluation and new information obtained since the evaluation was completed

4.3.2.1 Manufacture and formulation at manufacturer's sites also formulation of enzyme at downstream user sites

The evaluation concluded that the measures identified and applied are suitable and adequate providing they are adhered to.

For both enzyme manufacture and formulation, there is an emphasis on engineering controls and plant design to prevent or minimise exposure. Local exhaust ventilation (LEV) is recommended for operations where containment is not practicable. Respiratory protective equipment (RPE) is used as a secondary measure for specific tasks. Where enzyme granulates are processed, best practice guidance developed for the detergents sector (see section 4.3.4) recommends that process equipment is tested to demonstrate that significant physical damage to granulates which could result in release of enzyme dust will not occur. Comprehensive worker training programmes are in place. Regular air monitoring is undertaken to help confirm that plant controls are operating as intended; typically this is performed using high volume static sampling (see section 4.3.1). Supervisors monitor worker behaviour to ensure workers follow safe working practices. Health surveillance programmes are in place to identify workers with raised levels of enzyme specific IgE (induction of sensitisation) or work related respiratory symptoms. Procedures are in place to follow-up situations where monitoring data, health surveillance data or worker observations identify potential problems. Finally, the health and safety system is periodically audited to ensure that it remains effective. Recently the detergents sector commissioned a survey to check if the procedures described in its best practice guidance are routinely followed (Basketter *et al*, 2015). Around 100 manufacturing facilities situated across the EU were included. The survey found that all participating companies are meeting the standards set by industry best practice guidelines.

In addition to reviewing working practices, the survey analysed air monitoring and health surveillance data for the period 2006 - 2010. Air monitoring results were presented as numbers of measurements above and below in-house OELs which range between 6 – 15 ng/m^3 or 60 ng/m^3 depending on the enzyme and presence (or not) of surfactants. The mean number of results above the action level was 1919 per year, representing 0.65% of readings (no information was provided about which enzymes were measured). It was stated that the majority

of measurements are close to the limit of detection (no further information about this was provided). The survey identified a high degree of worker participation in health surveillance programmes which typically exceeds 95% of the workforce. The yearly rate of induction of sensitisation was found to be below 1% with 1 in 10 of those going on to develop symptoms of rhinitis or asthma. Similar rates of induction and the development of symptoms of rhinitis or asthma have been reported for enzyme manufacture.

Enzyme manufacture and formulation were not identified as potentially requiring further regulatory attention in the evaluation. The sector has clearly documented good practice guidelines which conform to the workplace risk management principles described in CAD and its parent directive the Framework Directive (89/391/EEC)[12]. It is not clear what further improvements would be made by imposing additional legislation. Since cases of occupational asthma do arise in workers manufacturing and formulating enzymes, these sectors should continue to be vigilant in monitoring the health of their workforces and identifying the circumstances leading to cases of sensitisation. In the light of this information, working practices should be periodically reviewed to confirm that best practice is being applied consistently at all sites and the working practices recommended in guidance are still the most appropriate to minimise worker exposure.

4.3.2.2 Industrial use as a processing aid

This covers the use of AA in several sectors including the manufacture of chemical substances/mixtures, textiles, leather, pulp and paper and waste water treatment. It also covers “cleaning in place” (CIP). This is a procedure that allows manufacturing plant (e.g. industrial food production equipment) to be cleaned internally without disassembly. Formulations used in these sectors typically contain 0.5% aep or less. Exposure scenarios for these activities provide generic advice on safe use which was deemed to be suitable and adequate in the evaluation. However, the fact that measureable levels of enzyme were reported for transferring activities in the textiles sector suggests that there is room for improvement in the way these measures are being implemented. The evaluation identified a possible need for sector specific good practice advice.

Since the evaluation was completed, the registrants have obtained new information about the use of enzyme solutions in rotary vacuum drum filtration processes. Typically, the filter cake that forms on the surface of the drum is washed before it is removed and sometimes this may be done using enzyme containing process water. Measurements of airborne enzyme levels associated with this use suggested that levels may be of a similar magnitude to those attained during enzyme production and detergent manufacture. It may therefore be helpful to provide specific guidance on minimizing enzyme exposure during this use.

New measurements have also been obtained for use in textile processes involving dipping and pouring. In the light of these new measurements, the registrants have updated the contributing scenario for treatment of articles by dipping and pouring with an instruction to use RPE unless the enzyme concentration is less than 0.005% or air sampling demonstrates that airborne enzyme concentrations are below the DMEL.

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[12] Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work

4.3.2.3 Professional use as a processing aid

This covers drain and hard surface cleaning. No concerns were identified for professional drain cleaning products that contain AA. AA-containing hard surface cleaning products can be used for large scale cleaning tasks such as cleaning surfaces and floors in institutional and industrial (I&I) kitchens or large scale food manufacturing vessels. Some of these products may be sprayed and RPE may be required to prevent inhalation of enzyme containing aerosols.

The evaluation raised questions about whether or not the workers and their supervisors who carry out the cleaning activities covered by these scenarios have sufficient information to make an informed assessment about the need to use RPE for specific tasks. Provision of task specific guidance designed to provide clear advice to these people about safe use of enzyme containing hard surface cleaning products would be helpful. It would also be very helpful to include advice on the correct use of RPE, including the need to perform face-fit testing if tight fitting RPE might be selected.

4.3.2.4 Professional use of AA-containing detergents

No concerns were identified for the professional use of AA-containing detergents (including prespotter sprays) in professional laundries or for the use of AA-containing detergents for I&I ware (crockery and cutlery) washing or hand dishwashing by professionals (e.g. restaurant or takeaway kitchens). In relation to the use of prespotter sprays in commercial laundries, these could potentially lead to aerosol formation if they are not formulated and used correctly. The registrants specifically exclude use of AA in products which are intended for spray application and hard surface cleaning unless the individual product has been tested in the form it is intended to be supplied. This is to ensure that in each case, the product design (e.g. viscosity) and delivery equipment (e.g. hand-held trigger spray) are suitable to ensure the user will not be exposed to levels above 15 ng/m^3 (the DMEL that has been applied for professional use) under normal and exaggerated conditions of use. The product specifications form part of the exposure scenario for that product. If there are any changes to the product design or delivery equipment, the product needs to be retested to ensure the modifications do not create the potential for exposure to levels above the DMEL. The testing protocol used in simulation studies for spray products has been published (Weeks *et al*, 2011).

4.3.2.5 Cleaning of medical devices

Measured data provided in registrations and obtained from published studies investigating exposure to enzymes in endoscope cleaning suites did not raise concerns for this use providing the operating conditions and risk management measures that are described in exposure scenarios for cleaning medical devices are implemented correctly.

In addition to the information in registrations, two small scale studies of enzyme exposure in endoscope cleaning suites have been published (Evans *et al*, 2013 and Adisesh *et al*, 2011). These studies are described in detail in the substance evaluation report (ECHA, 2016). In summary, it was found that a variety of cleaning methods were used across the endoscope cleaning units that were visited and this included working practices that allowed the formation of fine sprays of cleaning solutions close to the worker's head. RPE was not routinely used for endoscope cleaning. Also face fit testing was not routinely undertaken hence it is not clear if the RPE where it was provided was fully effective.

Personal and static sampling was performed to investigate the levels of enzyme exposure that were occurring in these endoscope cleaning suites (samples were analysed for protease using a method that detects enzyme activity). No enzymes were detectable in 10 out of 14 personal samples and 5 out of 11 static samples collected by Evans *et al* (2013). Where enzymes were detected, levels ranging from 8.9 - 66.7 ng/m^3 (8-hr TWA) were found in personal samples and 0.6 - 45.1 ng/m^3 (8-hr TWA) were found in static samples. These were all collected during manual cleaning in sinks (wet wiping, scrubbing and injecting enzyme cleaner). Surface wipes revealed the presence of surface contamination in 6 of the 7 units visited. The unit with the lowest levels of surface contamination performed wet surface cleaning throughout the day whereas other units only cleaned once per day. This illustrates the importance of regular cleaning in managing exposure to enzymes.

Adisesh *et al* (2011) also performed air sampling and took surface wipes at one hospital and their findings were consistent with those reported by Evans *et al* (2013).

Both Evans *et al* (2013) and Adisesh *et al* (2011) commented on the advice being disseminated to end users via safety data sheets (SDSs). No SDS contained information about a potential respiratory sensitisation hazard. One product supplier (downstream formulator) advised use of disposable absorbent pads around the sink to limit the spread of contamination and in some cases, product suppliers advised users to keep the endoscope under water whilst scrubbing off surface contamination. The extent to which this inconsistent provision of good practice advice contributed to the variations in housekeeping standards between endoscope cleaning units is not clear.

These studies demonstrate that good practices are not necessarily followed in relation to the use of enzyme containing products. This may be in part due to inconsistent communication of good practice advice from downstream formulators. Although airborne enzyme levels were generally found to be below the worker DMEL at the sites visited, this is not always the case. If poor working practices are adopted by someone working in a busy cleaning unit, they could experience many peak exposures that exceed the DMEL during their working day. This clearly represents a risk to their health. The evaluation concluded that the measures described in the exposure scenario are suitable and adequate and that the registrants are taking reasonable steps to support the dissemination of good practice advice through the supply chain. It may be useful to see if additional communication tools can be developed to improve the adoption of good working practices in endoscope cleaning suites.

4.3.2.6 Consumer use of enzyme containing products

No concerns were identified for any consumer use with the exception of the possible case where enzymes are included in hand dishwashing formulations. The concern arises not where such products are used as intended by the manufacturers but where they are used for other foreseeable uses e.g. to make bubble blowing mixtures for children.

It is not clear how widely enzymes are used in hand dishwashing liquids for consumers but such products are on the market and this use may increase in the future. To help understand if this foreseeable use could create a risk, the registrants have performed new studies to investigate potential exposure under worst case conditions (use indoors in an unventilated room with an automatic bubble blowing toy). A consumer survey was also performed to find out how often these worst case conditions could arise in practice. The results showed that under worst case conditions, levels of enzyme in air could rise to levels seen in liquid

enzyme manufacturing facilities. However, these conditions were only rarely likely to be replicated by consumers (in a consumer survey, 2% of 1552 respondents from the UK, Germany and the United States of America indicated they might use home-made bubble blowing mixtures under worst case conditions).

The possibility that worst case conditions may occasionally be replicated by consumers raises a concern. To put this concern into context, it is relevant to note that the prevalence of respiratory sensitisation in workers at liquid enzyme production facilities, where background concentrations in workplace air of up to 60 ng/m^3 are measured, is around 10%. Of these, 10% may go on to develop symptoms of allergic rhinitis or asthma. These workers will be exposed daily for several hours each shift. No enzyme-related allergic symptoms have been recorded among supervisors and managers who enter enzyme production areas occasionally but not daily. The exposure to managers and supervisors is more likely to replicate that from occasional bubble blowing. This suggests that even if enzyme-containing hand dishwashing liquids are used for bubble blowing under worst case conditions, there appears to be a low likelihood that enzyme-related allergic symptoms may develop as a consequence of this activity.

Based on the new information obtained by the registrants, the exposure scenario for consumer hand dishwashing liquids has been amended to set an upper limit of 0.015% aep for the use of AA in hand dishwashing products and now proposes that additional instructions for use are included on product labels. As a precaution, these requirements have been extended to hand dishwashing liquids intended for professional use.

4.3.3 Background information on occupational exposure limits for enzymes

4.3.3.1 Use of occupational exposure limits to manage risks

Occupational exposure limits (OELs) are risk management tools that help the occupational hygiene community identify the most appropriate control strategy for specific substances. In the early 1970's the ACGIH established a Ceiling TLV of 60 ng/m^3 for the protease subtilisins. The ACGIH recommends Ceiling limits where it is necessary to avoid transient excursions above the identified limit. When this number was identified, it was not intended to represent a "safe" level of exposure but was the lowest level that could be achieved by detergents manufacturers at that time. The ACGIH recommended limit has subsequently been adopted into national workplace legislation in several countries, in most cases as a Ceiling limit (see table 7). In 2000, the UK reviewed its national limit for subtilisins which was based on the subtilisins TLV and concluded that the limit should be lowered to 40 ng/m^3 (8-hr TWA). This lower value was adopted into UK national workplace legislation in 2005. The limit applies to all workplace use of proteases covered by CAS numbers 1395-21-7 and 9014-01-1. It represents a level that can be achieved where good occupational hygiene practices are followed. Although it is usual to establish short-term limits for respiratory sensitisers to limit potential short-term peak exposure, the UK did not set a short-term limit for subtilisins because it was not possible to measure personal exposure accurately over the 15-minute reference period.

Table 7: OELs for subtilisins reported for EU Member States [13]

[13] Information obtained from the GESTIS International Limits Values database (accessed on 13 January 2017) (http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx)

Country	8-hr TWA limit (ng/m³)	Short-term limit (ng/m³)	Remarks
Belgium	60		
Denmark	60	60 (ceiling value)	
Ireland	60	60 (ceiling value)	
Spain		60	Sen notation
Sweden	1 glycine unit/m³	3 glycine units/m³ (ceiling value)	
UK	40		Sen notation

Although limits for other enzymes have not been established in national or EU-wide workplace legislation, the 60 ng/m³ level is used by companies manufacturing enzymes and formulating enzyme containing products as a benchmark applicable to all enzymes to identify tasks where workers may need to wear RPE to supplement the engineering controls that are in place. Some companies have adopted more stringent benchmarks. For example, the major European detergents manufacturers use limits ranging between 5 and 15 ng/m³ for AA and between 5 and 20 ng/m³ for other enzymes (Basketter *et al*, 2010). These lower limits have been chosen because it is considered that the surfactants that are used in detergent formulations may enhance the allergenic activity of enzymes and the presence of proteases may enhance the allergenic activity of other enzymes. They are not identified as “safe” levels of exposure. Workplaces adopting these “in-house” limits typically use static monitoring to track airborne enzyme levels and prompt corrective action where necessary.

4.3.3.2 Challenges for setting legally binding OELs for enzymes

When the UK revised its national OEL for subtilisins, it also examined the possibility to set a national OEL for AA. The work covered AA of fungal and bacterial origin covered by the CAS number 9000-90-2. Since it was clear that no threshold of effect could be identified for these forms of AA, if a limit was to be established it would have to be set at a level that reflected good working practices.

In order to introduce OELs into legislation, it is a requirement that the value chosen is achievable across all sectors where the limit will apply and that the value can be reliably measured for the purposes of demonstrating compliance. Ideally, OELs should relate to exposures measured using personal monitoring methods.

At the time, no suitable data were available to identify personal exposures corresponding to good working practices across all sectors where AA is in use. Therefore, before a limit could be set, it would be necessary to conduct a measurement survey across all sectors of industry to gather this data. It became apparent that measuring exposure to AA would not be straightforward.

It is possible to measure airborne enzyme levels using methods that detect enzyme activity or immunological methods that detect specific protein epitopes. Since AA is used in sectors where other substances with this enzyme activity are present (AA is used as a flour improver in bakeries to supplement the AA activity present in the flour itself) a method based on detecting enzyme activity in air was not considered to be useful. A monoclonal based immunoassay was therefore developed that would allow airborne AA from fungal sources to be distinguished

from that arising from cereal flours (Elms *et al*, 2001). However, immunological methods have the limitation that the antibodies are specific for specific protein epitopes. Different antibodies may be required for AA obtained from different organisms. Also, it is not clear if the results obtained using an immunoassay developed by one organisation would be directly comparable to the results obtained using a different immunoassay developed by a separate organisation. This means that while it is possible to use immunoassays in exposure surveys, they may not be suitable for use in compliance monitoring or enforcement action.

There is a separate issue about the possibility to reliably measure personal exposures. Although it is possible to detect AA in the low ng/m^3 range, it can be difficult to obtain sufficient material from short-term samples collected at the low flow rates that are possible with personal sampling devices to measure sufficiently accurately for the purposes of compliance monitoring and enforcement action[14].

Given these challenges, it was decided not to progress work to develop a legally binding OEL and instead to focus on good practice guidance.

4.3.4 Current information on safe use

As a minimum, information on hazard and safe use should be provided where there is a legal obligation to provide safety data sheets. This applies to substances and mixtures that are classifiable according to the CLP Regulation (EC) No 1272/2008. For AA, the concentration limit triggering the requirement to provide safety data sheets for mixtures containing this substance is 0.1%. This is accompanied by a requirement to identify the sensitising components in the mixture using statement EUH208.

Typically, mixtures produced by downstream formulators contain 0.5% or less aep in some cases much less[15]. This means that the legal obligation to provide safety data sheets may not apply to all formulations. Where there is no legal obligation, formulators may choose to provide safe use guidance in technical product information, but this will not necessarily adhere to a standard format and it is not known if the information will be presented in a form that is easy to understand by the recipient. No further information about the safe use information typically provided by downstream formulators was available during the preparation of this RMOA.

Enzyme containing products that meet the definition of a detergent according to the Detergents Regulation (EC) No 648/2004 and which are sold to the general public must indicate the presence of enzymes on the product label if they are included in the formulation. Unlike the use of EUH208, there is no concentration threshold attached to the labelling requirement specified in the Detergents Regulation, hence this information should be given on any enzyme containing detergent formulation. It is not clear if the people who use these products associate a “contains enzymes” flag with the need to avoid inhaling aerosols during use of the product.

There are some additional sources of advice on how to use enzymes safely:

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[14] These difficulties are likely to be encountered if the value of 0.9 mg/m^3 (8-hr TWA) provisionally identified by the Health Council of the Netherlands as a level of exposure to fungal AA derived from *Aspergillus oryzae* that is associated with 1% risk of induction is translated into a legally binding OEL.

[15] For example, information obtained by HSE during its review of the OEL for subtilisins indicated that the maximum concentration of this enzyme in laundry detergent powders was 0.05% (http://www.hse.gov.uk/aboutus/meetings/iacs/acts/130303/paper08.pdf , site accessed 6 October 2017). It is expected that levels of AA and other enzymes in laundry detergents will be similar.

4.3.4.1 Guidance from enzyme manufacturers

Novozymes, has developed a series of 9 training videos each lasting around 2 - 2.5 minutes covering:

- Enzymes and associated health issues
- Respiratory allergy
- Determination of enzyme allergy
- Product design and safety
- Safe handling
- Safety precautions
- Management of enzyme spill
- When to use RPE
- Personal hygiene and first aid

These are freely available via Novozymes website[16] and can be used by downstream managers and supervisors as part of the company training programme. They are mainly targeted at downstream formulators rather than end users of enzyme containing products, but it would be possible to extract some relevant advice for these end users.

4.3.4.2 Advice from trade associations

The International Association for Soaps, Detergents and Maintenance Products (AISE) publishes extensive guidance on safe handling of enzymes which is aimed at detergents formulators (AISE, 2015; AISE, 2014)[17]. They have also developed a series of webinars and presentations covering the following topics (the last two are only available as presentations):

- Introduction to enzyme safety
- Enzymes: Risk management measures
- Engineering controls: Safety and engineering teams
- Exposure monitoring: Safety, laboratory and quality managers, laboratory staff
- Health surveillance: Site managers, safety managers, occupational health
- Consumer safety: Product development, product safety
- Laboratory safety: Safety, laboratory and quality managers, laboratory staff

AISE has developed a poster that can be displayed in workplaces where enzymes are used[18]. It is mainly aimed at formulators and provides key messages about safe use of enzymes. It is currently available in English, Chinese, German, Italian, French, Japanese, Spanish, Portuguese, Dutch, Danish, Finnish, Arabic, Brazilian, Polish, Hindi, Russian and Indonesian and will be translated into other languages in due course.

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[16] http://www.novozymes.tv/channel/10795880/safety-material (site accessed on 6 October 2017)

[17] https://www.aise.eu/our-activities/standards-and-industry-guidelines/safe-handling-of-enzymes.aspx (aimed at detergent and cleaning industry – site accessed on 6 October 2017)

[18] https://www.aise.eu/documents/document/20160720120123-enzymes_poster_en.pdf (site accessed on 6 October 2017)

This trade association is also participating in initiatives aimed at developing safe use information for professional end users[19]. In collaboration with its Dutch national association (NVZ), it has produced so called Generic Exposure Information from Substances (GEIS) sheets which are now called Safe Use of Mixtures Information (SUMIs). These are aimed in particular at the institutional cleaning sector and are intended to simplify the way safe use information is provided for workers. Thirteen GEIS/SUMIs have been developed for uses described by PROC codes 1, 2, 4, 8a, 8b, 10, 11, 13 or 15. These documents are not specifically geared towards communicating safe use information for enzyme containing products and only provide the generic statement "*This product may contain sensitizing ingredients that may cause an allergic reaction in certain people. Section 15 of the SDS states these ingredients, when applicable to the product*". New GEIS/SUMIs for products containing enzymes are expected to be developed in the near future.

It is up to the formulators to decide if specific or dedicated advice needs to be provided for enzyme containing products. No particular advice on hazard and risk communication for enzyme containing products is provided in supporting guidance aimed at formulators preparing SUMIs and environmental H+S managers of cleaning companies needing to act on the information. However, AMFEP has produced guidance to help formulators identify the correct classification for enzyme containing mixtures[20].

The Association of Manufacturers and Formulators of Enzyme Products (AMFEP) also provides a guide to the safe handling of enzymes[21]. Like the AISE guidance it is aimed at detergents formulators but is shorter than the AISE guidance. AMFEP also produces some specific guidelines for medical device cleaning[22]. This corresponds to the advice provided in the REACH exposure scenario. The evidence provided in Evans *et al* (2013) suggests that where medical device cleaning is performed in accordance with the procedures described in this guidance, exposures can be reduced to levels where there is a low concern for human health. The AMFEP guidance includes a recommendation that the manufacturers of medical device cleaning products should develop specific advice to be provided to end users along with relevant products. The provision of product specific safe-use instructions which are designed to get relevant messages to the workers themselves will make an important contribution to ensuring enzyme containing products are used safely.

Recently AMFEP has also published two short documents providing safe use guidance for both the textile and the pulp & paper industry[23].

4.3.4.3 Other sources of guidance

[19] https://www.aise.eu/our-activities/product-safety-and-innovation/reach/safe-use-information-for-end-users.aspx (site accessed 6 October 2017)

[20] http://www.amfep.org/sites/default/files/Amfep%20Guidance%20in%20a%20Nutshell%20Classification%20of%20enzymes%20according%20to%20the%20CLP%20Regulation.pdf (site accessed 6 October 2017)

[21] http://www.amfep.org/sites/default/files/201407/Guide%20to%20the%20safe%20handling%20of%20industrial%20enzymes%20preparations%202013_0.pdf (site accessed 6 October 2017)

[22] http://www.amfep.org/sites/default/files/201511/Amfep%20guidance%20Safety%20in%20the%20use%20of%20enzyme%20containing%20reagents%20for%20medical%20device%20cleaning.pdf (site accessed 6 October 2017)

[23] http://www.amfep.org/content/occupational-safety (site accessed 6 October 2017)

McBride, a UK based company that produces household cleaning products including detergents, has published its enzyme management policy[24]. This could be used by other downstream users to help them develop their own site risk management policies. No other guidance documents have been identified.

4.3.4.4 Areas currently lacking targeted guidance

Looking across these sources of guidance, it is apparent that with the possible exception of the cleaning sector, very little information has been developed that is specifically aimed at small and medium sized enterprises (SMEs). It is possible that some guidance is being provided by formulators with the enzyme containing products that they supply, but this has not been identified by the internet searches performed during the preparation of this RMOA. Evans *et al* (2013) provides evidence that poor handling practices can be adopted where messages are not communicated effectively and that these poor practices can result in airborne levels of enzymes achieving sufficiently high levels to raise the possibility for the induction of sensitisation and elicitation of symptoms of allergy. The lack of clear information aimed at end users is therefore identified as a concern and one which the registrants recognise.

ECHA's Exchange Network on Exposure Scenarios (ENES) is aware that the supply chain has identified challenges relating to the way information from exposure scenarios is communicated downstream and is developing a range of tools to improve these communications. This work is at a relatively early stage but includes organisations representing suppliers (registrants) and downstream uses (including formulators). It is important that formulators take an active role in the dissemination of supply chain communications about safe use because they are best placed to get safe use information to the end users. Information should be presented in different formats to suit different target audiences including workers, also their managers and supervisors who may have to cover health and safety duties as part of a much larger portfolio of responsibilities. During the preparation of the RMOA, the registrants indicated that AMFEP is developing "Safety Cards" aimed at SMEs which will present safety data sheet information in a simple visual format. Attention should also be given to guidance provided for consumers to ensure products are used safely.

4.3.5 Alternatives

Elimination and substitution should always be considered as the preferred risk management options for high hazard substances. Enzyme technologies have been developed as an alternative to traditional chemical technologies, therefore one option for substitution would be to revert back to the older technologies that enzymes have replaced.

Enzymes such as AA are increasingly being used because they offer several benefits when compared with alternative substances for various processes. They have a very specific targeted activity meaning that good results can be achieved with small quantities without the damage to process equipment and product that can occur when harsh chemicals such as acids or alkalis are used. This benefit was commented on by Stiefel *et al* (2016) in relation to endoscope cleaning. Enzymes allow processes to take place at lower temperatures making a significant contribution to lowering energy consumption and process wastes are less

[24] http://www.mcbride.co.uk/media/51870/mcbride-enzyme-management-policy-2012.pdf (site accessed 6 October 2017)

damaging to the environment. For these reasons, enzyme technologies make a valuable contribution to sustainable production initiatives and green chemistry.

It is important to look broadly at the benefits and disadvantages of alternatives when identifying potential substitutes. Until alternatives that offer the same or greater benefits for the environment are available, substitution across all uses is not identified a goal for regulatory action for AA. However, companies that use enzymes should periodically review their use to confirm that suitable, safer alternatives are not available.

5 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

5.1 Need for (further) risk management

AA was included in the CoRAP and evaluated by the UK CA in 2015. AA is an enzyme and is classified as a respiratory sensitiser. There is evidence that workers who use enzyme containing products develop enzyme specific IgE (induction of sensitization) (Budnik *et al*, 2016). Although the number of cases of enzyme related occupational asthma reported to the UK work related ill-health reporting scheme, THOR, does not seem to reflect the numbers with enzyme specific IgE reported by Budnik *et al* (2016), cases are reported to the THOR scheme at a rate of 1-2 per year. Since AA containing products are manufactured and used across the EU, it is reasonable to conclude that the THOR data will reflect the situation in other EU MS. This suggests an ongoing concern which warrants attention. It is preferable to take a consistent approach across all MS and hence Union-wide action is justified.

The evaluation did not identify evidence that any of the registered uses for AA give rise to unacceptable risks where the use is performed in accordance with the operating conditions and risk management measures described in REACH exposure scenarios. However, a need was identified for additional guidance on safe use to help downstream users manage the risks appropriately.

The evaluation also identified a possible risk for consumers if hand dishwashing liquids containing AA (and other enzymes) are used for activities other than washing dishes (e.g. making bubble blowing liquids for children). New information obtained by the registrants after the evaluation was completed suggests that under worst case conditions, levels of enzyme in air could rise to levels seen in enzyme production facilities if bubble blowing solutions are made with enzyme containing hand dishwashing liquids. In light of this, the registrants have set an upper concentration limit in the exposure scenario and have proposed additional instructions for that can be included on product labels for both consumer and professional use hand dishwashing liquids.

The RMOA will therefore consider options to:

i) ensure that suitable good practice advice is developed and communicated to all workplace users of AA containing products; and,

ii) ensure that potential risks to consumers who may choose to buy hand dishwashing liquids containing AA are adequately managed taking into account all foreseeable uses.

5.2 Identification and assessment of risk management options

The following have been identified as potential options to address the identified concerns for workers and/or consumers:

- Amending the concentration limits that are applicable to AA (and other enzymes) under the CLP Regulation (EC) No. 1272/2008.
- The Detergents Regulation (EC) No. 648/2004.
- REACH (EC) No. 1907/2006.
- Options under CAD (98/24/EC).
- General Product Safety Directive (2001/95/EC).

5.2.1. Amending the concentration limits identified for AA in the CLP Regulation

A key element in the adequate communication of safe use information is the provision of accurate information about the hazardous properties of the substances and mixtures being used. Hazard communication is governed by the provisions of the CLP Regulation. It has been noted in the context of endoscope cleaning mixtures that SDSs are not identifying these mixtures as potential respiratory sensitisers. This is probably because the concentration of AA in the mixture is below the thresholds set by the CLP Regulation.

AA is currently listed in Annex VI of the CLP Regulation with a harmonised classification of Resp. Sens 1. This classification must appear on product labels where the substance is supplied as itself and in mixtures containing 1% or more of the substance. There is a further requirement for mixtures containing 0.1% AA or more to include the supplemental hazard statement EUH208 to alert those who know they are sensitised to this enzyme that it is present in the product. Warnings of respiratory sensitisation potential are not permitted for mixtures containing less than 0.1%.

While it is currently not possible to identify a clear threshold for induction or elicitation, the evidence suggests that these processes can occur at dose levels in the ng/m^3 range. This raises a concern that mixtures containing AA may present a risk for respiratory sensitisation at concentrations below the generic cut off value of 1% established in CLP for classification of mixtures as Resp. Sens. 1 and that it may be desirable for warnings to be provided for mixtures containing less than 0.1% AA. This could be achieved if the threshold for classifying mixtures containing AA was lowered.

If the threshold is lowered, this might expand the range of mixtures which are formally classified as potential respiratory sensitisers. Changing the hazard classification of mixtures is likely to stimulate formulators to revisit the safe use guidance that they supply and should prompt users to revisit their workplace risk assessments. This measure therefore has the potential to stimulate improvements in the dissemination of safe use information to workers. It is not clear if this measure would have an impact on the way consumers use enzyme containing products.

The CLP Regulation provides two options to lower the concentration limits for communicating on respiratory sensitisation hazard. This can be done by

establishing specific concentration limits for the substance in question or it can be done by making use of the Resp. Sens. 1A sub-category in which case, the generic cut off value for classification as Resp Sens would be 0.1%.

The possibility of establishing specific concentration limits is discussed in section 3.4.2.1.5. of the Guidance on the Application of the CLP Criteria. This states that:

"Respiratory sensitisers cannot be identified reliably on the basis of animal tests as yet, since no recognised validated test exists to determine sensitising potential and potency by inhalation. Therefore specific concentration limits (SCLs) cannot be set on the basis of animal data alone. Moreover, there is no concept available to set SCLs on the basis of human data for respiratory sensitisers."

No information has been identified for AA that could be used to advance thinking on this point sufficiently to allow SCLs to be established for this enzyme (unlike skin sensitisers, no criteria are available to indicate which information might be most relevant to use as a basis for establishing a specific concentration limit), hence this option does not seem viable in this case.

The criteria for making use of the Resp. Sens. 1A sub-category are outlined in Table 3.1.4 of the Guidance on the Application of the CLP Criteria[25]. Annex I: 3.4.2.1.1.3 states that substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals. The relevant sections of table 3.4.1 are reproduced here for convenience.

Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests (1). Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests (1). Severity of reaction may also be considered.
(1) At present, recognized and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.	

Therefore, in order to make use of the Resp. Sens. 1A sub-category, it would be necessary to demonstrate a high frequency of occurrence of cases in humans. In relation to this, the Guidance on the Application of the CLP Criteria notes that:

"High frequency and low to moderate frequency cannot be defined as specific concentrations or percentages for human study data because, when considering human evidence, it is necessary to take into account the size of the exposed population and the extent and conditions of exposure, including frequency. It is necessary, therefore, to reach a view on a case-by-case basis."

Given that AA is one of the enzymes included in laundry products supplied to consumers, the size of the exposed population is potentially very large. However, the exposure intensity will be very low for consumers. It may be better to focus on the information that has been obtained from studies in workers (described in

[25] https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5 (site accessed 20 September 2017)

section 3.2). The information that is available suggests that the number of confirmed cases of occupational asthma compared to the size of the population potentially regularly exposed at work will be small but there is no accurate information on how many workers are regularly exposed to enzymes and their exposure intensity. There are also no agreed quantitative criteria that might help to interpret this information if it was available. It is therefore questionable if sufficient information is available to consider allocation of AA into the Resp. Sens. 1A sub-category at this time. For this reason it is not expected that new regulatory action can be taken under the CLP Regulation.

5.2.2. Detergents Regulation EC No. 648/2004

Many of the products that are covered by this RMOA are subject to the provisions of the Detergents Regulation. Article 11(3) of this regulation requires enzyme-containing products meeting the definition of a detergent to carry information on the product label indicating the presence of enzymes in the product. It also requires the packaging to indicate instructions for use and any special precautions that must be taken:

"*The packaging of detergents shall indicate the content, in accordance with the specifications provided for in Annex VII A. It shall also indicate instructions for use and special precautions, if required.*"

For products sold purely for use by the industrial and institutional sector, this information could alternatively be provided in a technical data sheet, safety data sheet or similar that accompanies the product.

In the case where a REACH exposure scenario for products in scope of the Detergents Regulation includes a requirement for specific safe use instructions to be given on product labels, Article 11(3), may provide a legal basis to carry use instructions from an exposure scenario onto product labels for products sold to the general public. If formulators do not include on product labels use instructions recommended by REACH registrants in exposure scenarios covering consumer use of that product type, and if regulatory intervention is considered necessary to require the inclusion of this instruction by those formulators, action would probably need to be taken under the Detergents Regulation. It is not known if similar actions have been taken in the past in relation to the special precautions referred to in Article 11(3) therefore there may be no precedents for enforcers to call upon when taking such an action. Provisions in the Detergents Regulation therefore may potentially support the dissemination of safe use instructions to consumers for enzyme containing detergents. It is important that registrants ensure that all companies that might choose to formulate enzymes into detergents covered by this regulation are aware that they might need to add exposure scenario information into their own instructions for use and special precautions on product labels.

5.2.3 REACH

5.2.3.1 REACH Registration: duties under titles II and IV

REACH places a responsibility on registrants to update their registrations without undue delay when new information becomes available. Suppliers of substances on their own or in mixtures are also required to provide the recipient with "… available and relevant information about the substance that is necessary to enable appropriate risk management measures to be identified and applied …". REACH requires that this information is communicated to downstream users via extended safety data sheets. Additional communication tools are being developed

to improve the way information is communicated both up and down the supply chain.

The registrants have reacted to the concerns identified in the evaluation by:

- Obtaining additional information and measured exposure data to help characterise worker exposure (see section 4.3.2.2).
- Conducting additional simulation studies and consumer use surveys to help assess the potential risks for consumers if they use hand-dishwashing liquids for other foreseeable uses (see section 4.3.2.6).
- Updating exposure scenarios where new information indicates this is required (see sections 4.3.2.2 and 4.3.2.6)
- Actively working with downstream formulators (e.g. detergents manufacturers) to develop a range of tools to improve the way safe use advice from the exposure scenarios is communicated to downstream users (see section 4.3.4).

These actions demonstrate that the registrants are fully engaging with the registration process and duties to provide safe use information. So far, the tools that have been developed to provide guidance on safe use have tended to be directed at the detergents manufacturing sector and cleaning. The evaluation concluded that it would be useful to supplement this with guidance targeted at additional sectors beyond cleaning.

In developing sector specific best practice guidance, it would be useful to consider if processes/ tasks could be designed differently to prevent release of enzymes at source thereby avoiding the need to use personal protective measures. Where this is not possible it would be useful to consider if RPE should be used even for situations where the worker DMEL of 60 ng/m^3 is not likely to be exceeded, but there is the potential for workers to inhale airborne enzyme.

It should be noted that any best practice guidance which is developed must be based on the measures described in the relevant exposure scenario and in turn, exposure scenarios should always reflect the latest thinking on best practices in each sector. Providing exposure scenarios are kept up to date by the registrants, the implementation of best practice by downstream users can be enforced using the provisions of REACH Article 37(5) which requires downstream users to apply appropriate measures to control risk.

It may also be possible to take enforcement action against workplaces where insufficient/inappropriate controls have been applied using national worker protection legislation.

Providing the current levels of engagement continue, the actions being taken to fulfil REACH duties under titles II and IV have the potential to provide the necessary good practice guidance for all workplace users of AA-containing products.

At this time, no additional actions appear to be necessary to manage possible risks to consumers.

During the preparation of this RMOA, the SUMIs that are available for the cleaning sector and other SUMIs that have been presented at meetings of the Exchange Network on Exposure Scenarios (ENES) were examined. Some initial reactions are provided here to help the future development of communication tools which are aimed at SMEs.

It is important that information is provided using a variety of communication media and that the language which is used is pitched at a level suitable for the

intended audience. It may be helpful to link simple guidance to specific products and tasks so that it is explicitly clear which guidance should be referred to in each situation. The guidance needs to be clear about the potential hazards of the product, preferably without requiring the recipient to consult other documents such as safety data sheets (even if there is a legal requirement to provide these documents). Including pictorial information such as icons to represent items of protective clothing that may be worn can be helpful, but it is also important that the recipient knows that they should see if there are other ways to manage the risks which avoid the need to use personal protective equipment (PPE) since this should always be seen as the least preferable risk management option. It is also important that icons do not inadvertently direct the recipient to choose inappropriate equipment. For example, a frequently used icon for RPE shows a worker wearing a tight fitting face mask, but this may not be the right type of mask for all workers performing a particular task or for all of the tasks for which a particular product may be used. Ideally if guidance indicates a need to use RPE, links should be provided to advice on how to select the right RPE for the task and person and how to use the RPE correctly to ensure that the levels of protection that have been assumed for this measure can be achieved in practice.

5.2.3.2 Identification as a substance of very high concern, SVHC (first step towards authorisation)

Authorisation is a potentially powerful tool that gives authorities the opportunity to examine each use for a substance and specify the conditions under which the use takes place. It could be argued that this option provides a means to ensure specific good practice instructions are available for every permitted use. Authorisation is only available for substances that meet the criteria for identification as an SVHC as described in Article 57 of REACH. As a respiratory sensitizer, AA potentially meets the Art 57(f) criteria as a substance of equivalent concern[26] (though it is not universally accepted that respiratory sensitisers present an equivalent level of concern to carcinogens, mutagens and reproductive toxicants[27]). AA also fulfils the other criteria for substances of potential interest under the SVHC Roadmap 2020 (see table 8).

Table 8: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?	✓*	
b) Registrations in accordance with Article 10?	✓	
c) Registrations include uses within scope of authorisation?	✓	
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?	✓	

[26]A detailed assessment to demonstrate equivalent level of concern has not been performed because identification as an SVHC is not seen as a necessary action for amylase, α-.

[27] http://www.cefic.org/Documents/IndustrySupport/REACH-Implementation/Guidance-and-Tools/Cefic-Position-on-Respiratory-Sensitisation.pdf (site accessed 6 October 2017)

* In the case of AA, Article 57(f) is considered potentially relevant. However, each proposal under Article 57(f) must be considered on a case-by-case basis. Arguments against the identification of enzymes as SVHCs have been raised in discussions at the Member States Committee[28].

Although respiratory sensitisers may be identified as SVHCs according to Art 57(f) this is not seen as an appropriate step for AA. Article 56(6)(b) disapplies the requirement to obtain authorisation for uses of substances listed on Annex XIV where these substances are present in mixtures below the concentration limits which result in those mixtures being classified as dangerous. In the case of a substance classified as Resp. Sens. 1, this threshold is 1%. Since most AA containing formulations currently supplied to downstream users typically contain a maximum of 0.5% aep, this removes most of the products for which additional safe use guidance is needed from the scope of this provision. Although reclassifying AA as Resp. Sens. 1A could lower the threshold to 0.1%, there is a lack of reliable information which would support such a change.

Inclusion on Annex XIV would also bring pressure on companies to substitute use of AA with alternatives. This is not identified as a desirable regulatory outcome given the many environmental benefits of enzyme technologies when compared with currently available alternatives (see section 4.3.5).

Identification as an SVHC and inclusion on Annex XIV may have the negative consequence that production of industrial enzymes and manufacture of enzyme containing products moves outside the EU (particularly since these are the activities that will be targeted rather than end use of formulations where there is the greatest need for clear guidance). If this happens, it may be harder to regulate the types of products that are imported, it will be harder to manage the communication of safe use information along the supply chain and authorities will have less oversight of products that are supplied for consumer use.

For these reasons, identification as an SVHC with eventual prioritization to Annex XIV is not seen as a useful risk management option for AA.

5.2.3.3 Restriction

Restrictions can be introduced where an unacceptable risk has been identified and it is necessary to take EU wide action to manage this risk. The evaluation did not identify uses giving rise to unacceptable risks.

In the case of workplace uses for AA, the concerns relate to inconsistencies in the way safe use information is communicated. No evidence has been identified that suggests AA cannot be used safely when suitable working practices are adopted, or that the suitable working practices that are required are not feasible for all potential users, hence there does not seem to be any justification to place restrictions on workplace uses for AA.

A possible risk was identified for consumers if they choose to use hand dishwashing liquids containing enzymes for other activities e.g. making bubble blowing mixtures for children. During preparation of the RMOA, new information was obtained by the registrants that helped to clarify the risk that this foreseeable use could create (see section 4.3.2.6). Based on the new information, there appears to be a low likelihood that enzyme-related allergic symptoms may develop as a consequence of this activity. There does not therefore appear to be

[28] See Annex VI in: https://echa.europa.eu/documents/10162/13578/meet_minutes_msc_27_en.pdf/d3387c55-875e-4d5d-bd36-505c135eaf9a (site accessed 6 October 2017)

any justification to consider restrictions on consumer use at present. However, it is important to make consumers aware that they should follow manufacturer's use instructions when using hand dishwashing liquids containing enzymes.

5.2.4. Options under CAD to develop and communicate suitable good practice advice to all workplace users of enzyme containing products

This option is not relevant to the concern identified for consumers.

CAD aims to provide a general framework to establish and enforce safe working practices where hazardous chemicals are used. The legislation describes the systems and in a general way the working practices that should be in place to meet the required minimum standards for worker protection. Although CAD requires a risk assessment to be performed where hazardous chemical agents are used, it does not specify precisely the risk management approach that should be taken for individual substances or how the results of risk assessments should be communicated. Within this legislation, legally enforceable OELs have been used as a tool to signal regulators' expectations about standards of control for specific substances. While a limit on its own will not improve the way good practice advice is communicated, guidance may be developed to help duty holders comply with a new limit. Setting a limit can therefore indirectly lead to improvements in the dissemination of information on good practice. As discussed in section 4.3.3, an attempt has been made to set a legally binding OEL for AA. Several difficulties were encountered and the decision was taken not to proceed. No information has emerged since this attempt to suggest that these difficulties can be resolved more easily now. It is therefore concluded that setting an EU-wide OEL for AA is likely to be a very resource intensive task and will not necessarily deliver the improvements in communication of suitable good practice advice to all workplace users of enzyme containing products that is needed. This option will not be considered further.

5.2.5 General Product Safety Directive

This option is not relevant to the concern identified for workers.

The GPSD includes measures designed to assure the safety to consumers of products that are supplied for consumer use and may foreseeably be used by consumers. Products that comply with this directive should be safe for normal and foreseeable conditions of use. In the case of hand dishwashing liquids containing enzymes, a possible concern was identified if such products are used to make bubble blowing mixtures. New information suggests low likelihood that enzyme-related allergic symptoms may develop as a consequence of this activity providing product formulations adhere to the requirements in the exposure scenario.

If there is a need to prohibit the supply of specific products in the future, it may be more effective to take such action under REACH since any EU-wide prohibitions on supply established under the GPDS are only valid for 1 year (article 13(2)). The GPDS is therefore not seen as a useful option and will not be considered further.

5.3 Conclusions on the most appropriate (combination of) risk management options

The concerns that were identified during the substance evaluation of AA related to the need to provide further good practice guidance to workers and a concern

relating to foreseeable uses for consumer hand dishwashing liquids containing enzymes.

For workers, none of the options for formal regulatory action that have been identified seemed able to provide the additional good practice communication that is needed. Industry-led initiatives do have the potential to achieve the identified aims. It is therefore recommended that the following actions should be initiated:

- Enzyme suppliers and product formulators should continue to work together to develop a range of communication tools that will help end users of products containing AA (and other enzymes) understand the risks associated with these products and manage those risks appropriately.
- Based on the potential for exposure, it would be useful to prioritise guidance aimed at the textiles sector, use in rotary vacuum drum filtration processes, professional hard surface cleaning and cleaning medical devices.
- Over time it will be helpful to extend communications to all sectors where enzymes are used. When new applications are developed, alongside product development, it will be useful to develop a suite of safe use communication tools covering these new applications.

The evaluation did not identify specific concerns relating to the OCs and RMMs identified for manufacture and formulation of enzyme-containing products. Given that some workers in these industries are found with raised levels of enzyme specific IgE and a small percentage develop symptoms of occupational rhinitis and/or asthma, it is recommended that working practices are regularly reviewed to ensure that best practice is being applied consistently at all sites and that the working practices recommended in best practice guidance are still the most appropriate to minimise worker exposure. For example, it may be possible to design processes/ tasks differently to prevent release of enzymes at source. Where this is not possible, it may be useful to consider the use of RPE even for situations where the worker DMEL of 60 ng/m^3 is not likely to be exceeded, but there is a likelihood that workers could still inhale airborne enzyme.

For consumer use, new information obtained by the registrants suggests that under worst case conditions, if bubble blowing solutions are made with enzyme-containing hand dishwashing liquids, levels of enzyme in air could rise to levels seen at enzyme production facilities. In light of this finding, the registrants set an upper concentration limit in the exposure scenario and have proposed additional instructions for use that can be included on product labels for both consumer and professional use hand dishwashing liquids. The RMOA has identified provisions in Article 11(3) of the Detergents Regulation which may provide a legal mechanism to include this information on product labels for products sold to the general public. Registrants should ensure all formulators are aware of relevant instructions to be included on labels for enzyme-containing hand dishwashing liquids.

In the future it may be desirable to review the availability of guidance and the extent to which downstream users are adopting best practices, also to check labelling instructions on consumer hand dishwashing products containing enzymes to ensure appropriate instructions are given. The time frame for such a review will depend on the priority that is given to the risk management of AA (and other enzymes) compared with other substances. One factor will be the extent to which cases of ill-health continue to be reported.

5.4 References

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NOTE: This annex contains confidential information

ANNEX I – CONFIDENTIAL INFORMATION

This annex is for the provision of confidential information, where it is considered necessary to include it.