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AMFEP Fact Sheet on Enzymes and the EU Regulation on classification, labelling and packaging of substances and mixtures (EC No 1272/2008, “CLP Regulation”)

1. Introduction

The previous AMFEP Fact Sheet on Enzymes and the CLP Regulation (AMFEP /09/73) contained general information on the harmonized classification of enzymes under the EU Regulation on classification, labelling and packaging of substances and mixtures (Regulation (EC) No 1272/2008, “CLP Regulation”), which entered into force on 20 January 2009.

The present paper updates and extends the Fact Sheet, describing how AMFEP implements the CLP requirements for enzyme products.

The CLP Regulation applies and implements the general principles of the United Nations Globally Harmonized System (GHS) of Classification and Labelling of Chemicals. The purpose is to align EU legislation with the GHS requirements to ensure that the same hazards of chemicals will be described and labelled in the same way all around the world. The following link provides information on how the CLP classification works:

http://ec.europa.eu/enterprise/reach/ghs/index_en.htm

Classification criteria are largely in line with the current EU system but GHS introduces new terminology and labelling e.g. new pictograms and precautionary statements. It keeps the scope as close as possible to the existing legislation and ensures consistency with the transport legislation. It will also affect other obligations in EU legislation (downstream legislation) which refer to classification such as Safety Data Sheets set in REACH, Detergent Regulation, EU Ecolabelling schemes etc.

The CLP Regulation takes over and converts Annex I of the Dangerous Substances Directive (DSD; 67/548/EEC¹) to Annex VI of the CLP Regulation², hereby listing the existing harmonized classification and labelling of substances according to the GHS. Carcinogenic, mutagenic and reprotoxic (CMR) substances and respiratory sensitizers will be subject to harmonized classifications under CLP.

Industry must follow the existing harmonised classifications of enzymes, including irritancy classifications, unless a proposal for classification change has been accepted by the European Chemicals Agency (ECHA). A re-classification proposal (Annex XV dossier) for hazard properties

(toxicological endpoints) included in the existing harmonised classification e.g. irritancy can only be submitted by a Member State competent authority. For endpoints not covered, Industry can

¹ As amended up to the 31st ATP (Commission Directive 2009/2/EC of 15 January 2009)

² As amended up to the 1st ATP (Regulation (EC) No. 1272/2008 of 5 September 2009)

make a proposal. In connection with preparing for REACH registration of enzymes, registrants will review available data on relevant enzyme types in the Substance Exchange Information Fora (SIEFs) and may consider if there is a need for revised harmonised classification. Further detailed guidance is available from ECHA.

The CLP Regulation will, after a transitional period, replace the current rules on classification, labelling and packaging of substances (DSD) and preparations (Dangerous Preparations Directive DPD; 1999/45/EC).

2. Enzymes in Annex VI of the CLP Regulation and in EINECS

Enzymes are a specific subcategory of Unknown or Variable composition, Complex reaction products or Biological materials, also called UVCB substances. They shall be identified in accordance with REACH guidance on identification³.

There are approx. 400 enzymes in EINECS. The 17 enzymes in CLP Annex VI do not cover all enzymes in EINECS but only contains those enzymes that were already present on Annex I of DSD. The naming of enzymes under REACH goes beyond the EINECS/CAS (Chemical Abstracts Service) entry and is based on the IUBMB nomenclature, where the catalytic activity is the key parameter. We linked the 17 enzymes in CLP Annex VI to EINECS entries and the IUBMB nomenclature in Appendix I.

The harmonized classification of the 17 enzymes is listed in Appendix II of the present document.

All these are classified and labelled as “Respiratory sensitizers (Hazard Category 1): H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled” and will be labelled with the ‘torso’ pictogram. The thresholds for mixtures containing sensitizers – 1% hazard warning and 0.1% allergy warning – remain unchanged under the CLP Regulation.

Subtilisin and other proteases may have additional classifications. The subtilisin harmonised classification is STOT SE 3, Skin Irrit. 2, Eye Dam. 1, Resp. Sens. 1. According to the REACH dossier submitted by AMFEP members subtilisin is classified in addition Acute Tox. 4, Aquatic Acute 1. CLP translation of ‘Eye Dam. 1 means a reduction of the cut-off limit from 10 to 3% compared to the previous DSD/DPD ‘serious eye damage’, and may result in a ‘corrosive’ pictogram above this limit. With regard to transport regulations, Eye Dam. 1 will not lead to a ‘dangerous goods’ status. However Aquatic Acute 1 may lead to a ‘dangerous goods’ status based on the concentration of subtilisin in the mixture.

It is AMFEP’s opinion based on existing toxicological data (see e.g. HERA⁴) that enzymes not covered by the 17 enzyme entries should be classified as Respiratory Sensitizer Category 1 by analogy.

In addition some proteases should also be classified as irritants. A detailed discussion of the irritation potential is however not the scope of the present document as it is specific for each enzyme. More information can be found in the UN-GHS classification table⁵ and AMFEP’s position⁶ on the 2nd Adaptation to Technical Progress (2nd ATP) of the CLP as laid down in Commission Regulation (EU) No 286/2011 which entered into force on 19 April 2011.

³ ECHA, “Guidance for identification and naming of substances under REACH”, 2007, section 4.3.2.3

⁴ HERA risk assessment on Protease, <http://www.heraproject.com/RiskAssessment.cfm?SUBID=22>, and HERA risk assessment on Amylase/Lipase/Cellulase, <http://www.heraproject.com/RiskAssessment.cfm?SUBID=38>.

⁵ UN-GHS classification table, http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

⁶ See Amfep/12/03: www.amfep.org/Amfep-12-03-Enzymes-and-criteria-of-respiratory-sensitizers-in-the-2nd-ATP-to-CLP.pdf

3. Enzyme calculations for classification of mixtures

Enzymes are in general considered to be of low toxicity with the exception of the allergenic potential by inhalation, and the limited irritation effects of some proteases at high concentration.

When enzymes meet the criteria laid down in “Safety evaluation of technical enzyme products with regards to the REACH legislation”⁷, the non-enzymatic constituents are considered safe and do not contribute to classification. Therefore active enzyme protein shall be used as basis for classification of enzyme products⁸.

Hazardous mixtures containing sensitisers at concentrations above 1% are classified and a warning label is required. Also, when a mixture contains at least one sensitiser in a concentration equal to or greater than 0.1% it must be labeled: ‘Contains (name of sensitising substance). May cause an allergic reaction.’

If enzyme blends are used, the relevant enzyme(s) should be mentioned. In these cases the requirement ‘at least one substance’ allows calculation based on one component exceeding 0.1% only. Thus, the sum of declared enzyme proteins might exceed 0.1% without need for allergy labelling.

Where enzymes of similar catalytic activity (i.e. belonging to the same IUB EC, CAS and EINECS numbers or belonging to the same enzyme type as listed in Annex I to Dir. 67/548/EEC) are used in a formulation, the levels of these enzymes is considered to be additive, unless there is evidence from immunochemical/immunological testing that they induce specific responses and can consequently be considered as separate entities.

Please notice that the enzyme substance defined under REACH shall be used for tonnage calculation. The Enzyme Reach Consortium provides guidance⁹.

4. Notification and Timing for labelling

According to the CLP Regulation (Article 40) and REACH Regulation (Article 113), a manufacturer or importer¹⁰ will have to notify substance identity and classification and labelling to ECHA¹¹, if a substance is:

- classified as hazardous under CLP and placed on the market, irrespective of the tonnage
- subject to registration under REACH (≥ 1 tonne/year) and placed on the market
- classified as hazardous under CLP and is present in a mixture above the concentration limits specified in Annex I of CLP or as specified in Directive 1999/45/EC, which results in the classification of the mixture as hazardous, and the mixture is placed on the market

⁷ ERpC/09/06, <http://enzymes-reach.org/documents.html>

⁸ See AMFEP Statement Enzyme Classification (Amfep/12/02): <http://www.amfep.org/Amfep-12-02-Statement-enzyme-classification-JAN2012-main.pdf>

⁹ Calculation of Tonnage for Enzyme Substances (ERpC/09/05, <http://enzymes-reach.org/documents.html>)

¹⁰ Chemical companies cannot use their REACH ‘Only Representatives’ (ORs) or ‘Third Party Representatives’ (TPRs) to submit classification and labelling notifications on their behalf to ECHA. Agency officials confirmed at ECHA’s third stakeholder day that this is the legal advice that they had been given by the European Commission on the grounds that the CLP Regulation does not mention ORs or TPRs. As a result, only manufacturers or importers can submit notifications. However, CLP allows for such companies to submit notifications in groups and there is no definition of such groups. For example, SIEF members, supply chains or even industry associations could decide to submit a notification as a group, as long as the identity of all companies involved in the notification is provided.

¹¹ http://echa.europa.eu/clp/inventory_notification/notification_who_en.asp

A hazardous substance placed on the market on its own or in a mixture must be notified within one month after being placed on the market. This includes hazardous substances which have already been manufactured before 1 December 2010, but which have not been placed on the market before (applicable substances already on the market before 1 December 2010 had to be notified to ECHA by 3 January 2011)

Thus a manufacturer or importer of enzymes preparations will have to classify enzymes and notify classification to the Agency, if enzymes meet the above criteria¹². According to the CLP text food or feeding stuffs which are in the finished state, intended for the final user are exempt from notification. AMFEP's conclusion is that we consider this only to be true when they are to be sold directly to a final user (the detail customers, farmers), but not when sold business-to-business.

If classification and labelling designations are submitted as part of REACH registration dossiers, they do not need to be separately notified.

A substance or mixture contained in packaging should be labeled according to CLP no later than 01 December 2010 and 1 June 2015 respectively. In addition, until 1 June 2015, the classification of a substance according to DSD must be provided in the Safety Data Sheet (SDS), in addition to the CLP classification. This will both apply to SDSs for substances on their own and to SDSs for mixtures containing these substances.

5. Executive summary

Enzymes possess respiratory sensitization potential regardless of the catalytic activities. All enzymes must therefore be classified as “R42: May cause sensitization by inhalation” in accordance with Dangerous Substances Directive (67/548/EEC) and “Respiratory sensitisers (Hazard Category 1): H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled” in accordance with CLP Regulation. The threshold concentration for classification & labelling with pictogram is 1 % (per individual enzyme), and for allergy warning is 0.1%, based on active enzyme protein (aep).

In accordance with CLP Regulation, a manufacturer and importer will under certain conditions have to notify the Agency (ECHA, the European Chemicals Agency) if a substance is classified as hazardous - irrespective of the tonnage of substance imported or manufactured. Thus a manufacturer and importer of enzymes will have to notify the above enzyme classification and identity to the Agency.

LEGAL NOTICE:

This Fact Sheet is meant as guidance only. The Fact Sheet is published by AMFEP in order to assist its members in their efforts to understand and comply with the CLP Regulation. Please be reminded, however, that the CLP Regulation is the only authoritative legal text and that this policy does not substitute legal or otherwise expert advice. AMFEP and its members do not accept any liability for use of this policy or for activities contemplated and carried out under this policy.

¹² Some enzyme products are exempted from these requirements (CLP regulation Art. 1 and Art. 39).

Appendix I: Enzyme entries on Annex 1 of Dir. 67/548/EEC versus enzyme identification under REACH



CLP-IUBMB_final.xls

Appendix II: Enzymes on Annex 1 of Dir. 67/548/EEC and Annex VI of EC Regulation No 1272/2008

Enzyme	CAS no.	EINECS No	Present EU classification (Annex I) Directive 67/548/EEC,		Danger Symbol	CLP classification (Annex VI)			Signal word
			R-phrase	S-Phrase		H-class/cat. code	Hazard statement	Pictogram	
Amylase, α -	9000-90-2	232-565-6	R42	S(2),S22,S24,S36/37	Xn	Resp. Sens. 1	H334	GHS08	Danger
Amylases with the exception of those specified elsewhere in this Annex	-----	-----	R42	S(2),S22,S24,S36/37	Xn	Resp. Sens. 1	H334	GHS08	Danger
Bromelain, juice	9001-00-7	232-572-4	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT* SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Cellobiohydrolase, exo-	37329-65-0	253-465-9	R42	S(2),S22,S24,S36/37	Xn	Resp. Sens. 1	H334	GHS08	Danger
Cellulase	9012-54-8	232-734-4	R42	S(2),S22,S24,S36/37	Xn	Resp. Sens. 1	H334	GHS08	Danger
Cellulases with the exception of those specified elsewhere in this Annex	-----	-----	R42	S(2),S22,S24,S36/37	Xn	Resp. Sens. 1	H334	GHS08	Danger
Chymotrypsin	9004-07-3	232-671-2	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Ficin	9001-33-6	232-599-1	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Glucosidase, β -	9001-22-3	232-589-7	R42	S(2),S22,S24,S36/37	Xn	Resp. Sens. 1	H334	GHS08	Danger
Laccase	80498-15-3	420-150-4	R42	S(2), 23-45	Xn	Resp. Sens. 1	H334	GHS08	Danger

Papain	9001-73-4	232-627-2	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Pepsin A	9001-75-6	232-629-3	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Proteases with the exception of those specified elsewhere in this Annex	-----	-----	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Proteinase, microbial neutral	9068-59-1	232-966-6	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Rennin	9001-98-3	232-645-0	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger
Subtilisin	9014-01-1	232-752-2	R37/38,R41,R42	S(2),S22,S24,S26,S36/37/39	Xn	STOT SE 3 Skin Irrit. 2 Eye Dam. 1 Resp. Sens. 1	H335 H315 H318 H334	GHS08 GHS05 GHS07	Danger
Trypsin	9002-07-7	232-650-8	R36/37/38,R42	S(2),S22,S24,S26,S36/37	Xn	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Resp. Sens. 1	H319 H335 H315 H334	GHS08 GHS07	Danger

*STOT = Specific Target Organ Toxicity