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Re: Enzymes and criteria of respiratory sensitizers in the 2nd ATP [1] to EU Classification, Labelling and Packaging (CLP) Regulation [2]

1. Subdivision of respiratory sensitizers in Table 3.4.1

The second Adaptation to Technical Progress (ATP) to the EU Classification, Labelling and Packaging (CLP) Regulation introduces sub-categories for respiratory sensitizers, discriminating between strong sensitizers and other sensitizers.

Sub-category 1A and 1B shall be used where documentation/expert justification makes it possible to classify sensitizers as:

Sub-category 1A:

A high frequency of occurrence in humans;
or a probability of occurrence of a high sensitization rate in humans based on animal or other tests .
Severity of reaction may also be considered.

Sub-category 1B:

A low to moderate frequency of occurrence in humans;
or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests.
Severity of reaction may also be considered.

If sub-categories 1A and 1B cannot be justified, a substance can be classified as Category 1 only.

<u>Enzymes</u>

REACH defines that the primary identifier for enzymes is catalytic activity defined by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB). There are approximately 400 enzymes listed in EINECS. Of those, 17 enzymes (13 enzymes on EINECS, 1 enzyme on ELINCS and 3 enzyme groups) are in Annex VI of CLP regulation. The common harmonized classification of the 17 enzymes is as respiratory sensitizers.

[1] Commission Regulation (EU) No 286/2011 of 10 March 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures

[2] Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation) is available in the following languages

Enzymes regardless of the catalytic activities are potential respiratory allergens, whereas the weight of human evidence indicates that enzymes are not skin sensitizers (Ref. 1, 2, 3, 4). All enzymes must therefore be classified as respiratory sensitizers (Ref. 5), "H334: Hazard Category 1: May cause allergy or asthma symptoms or breathing difficulties if inhaled" in accordance with the CLP Regulation.

Unlike skin sensitizers which can be classified as strong/weak by using the ranking from the Local Lymph Node Assay (LLNA), predictive animal models for respiratory allergy in humans do not exist.
Therefore, the available clinical studies are the only basis for enzyme classification with respect to respiratory sensitisation. When respiratory sensitisers are ranked based on human data, it relies on human exposure information considering magnitude and frequency of exposure and severity of response among exposed individuals during the actual use of the marketed (commercially) available product(s) (Ref. 6).

Commercially available detergents contain typically 0.01 % to 0.09% active enzyme protein derived from enzymes with various catalytic activities included in the detergent (Ref 1, 4). A recent publication (Ref. 7) summarises clinical data with regard to respiratory type 1 allergy in consumers of laundry products from a range of sources collected over the past 40 years. From 1977, the prevalence of enzyme specific IgE antibody in clinical study subjects and employees from detergent manufacturers before occupational exposure , was found to be only 0.126% (14 positive out of a total of 11,078 people). However, at least 6 of the 14 cases could be questioned: In 3 cases, the positive IgE outcome could not be confirmed in a second test, and the skin prick test for allergic antibody performed pre-1992 was performed at a concentration of 500 µg/mL, which in other 3 cases is likely to be false positive responses. None of the 14 cases could be linked to the use and exposure to enzymes in laundry and cleaning products. Furthermore it was shown that even in the highly sensitive (selected) population of atopics, which were included in the clinical studies, the regular exposure to enzymes in laundry and cleaning products did not lead to either the development of enzyme specific antibody of type IgE or the development of any symptoms of respiratory allergy or diseases. The studies in reference 7 demonstrate that there is absence of any clinical important reactions. This is in accordance with the Technical Advisory Panel on Allergic Sensitization in the US Consumer Products Safety Commission who qualifies severity based on a "clinical important reaction" as one producing substantial illness (i.e.; physical discomfort, distress, hardship, functional and structural impairment) (Ref. 6).

Due to current formulation e.g. in liquids or non-dusting granulates, normal enzyme exposure of consumers associated to laundry products is significantly less than 1 ng/m³ which is in fact taken as a threshold based on a benchmark approach to exclude allergic symptoms (Ref. 1). Based on a study with a spray pre-treater an even higher derived minimal effect level (DMEL) for sensitization of 15 ng/m³ is suggested (Ref. 2) which is significantly higher than the expected consumers' normal exposure. This in conjunction with the low prevalence of enzyme specific IgE antibodies mentioned above suggests that the risk of developing clinical symptoms of respiratory allergy in the general population is negligible.

A recent publication (Ref. 12) examined whether a sub-categorisation of protein and/or chemical respiratory allergens was realistic and/or feasible. The conclusion drawn was that, on the basis of the currently available information, potency categorisation for respiratory sensitisers was premature and could potentially be misleading.

2. Para 3.4.4.2 of UN GHS – Label provision

The current label provision as given in Annex II 2.8 of the CLP should be expanded to subdivisions i.e. 0.01 % for sub-category 1A and 0.1 % for sub-category 1B.

Enzymes
It is concluded that the elicitation concentration of enzymes is even higher than the induction concentration based on the practical experience with occupational allergy towards industrial enzymes (Ref. 2, 8, 9).

As described in the clinical studies mentioned in the previous section, low frequency of occurrence in human and absence of clinical reaction are demonstrated to the general population who are exposed to commercial detergents containing 0.01 – 0.09 % enzymes.

We conclude that the present classification concentration limit for Category 1 or 1B, i.e. 0.1 % provides sufficient protection against enzymes.

3. Overall conclusion on enzymes

Based upon the currently available information including human data collected for over 40 years it is concluded that potency sub-categorisation for respiratory sensitisers is premature and can potentially be misleading, therefore enzymes should be classified as Respiratory Sensitizer Category 1. The label provision of Category 1 also ensures sufficient level of protection against enzymes.

References

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