The European Commission's proposal for a Mixture Assessment Factor (MAF) is not appropriate for enzymes

AMFEP acknowledges the political will to address combination effects of some chemicals within the Chemicals Strategy for Sustainability (CSS). However, AMFEP objects to the introduction of a generic Mixture Assessment Factor (MAF) of 5 to be applied to any endpoints. AMFEP supports solutions that are tailored and targeted to minimise risks for human health and the environment based on the substance-specific use. For enzymes, AMFEP would like to provide arguments why a MAF will be disproportionate and how mixture effects are already taken into account in the current Derived Minimal Effect Level (DMEL).

The toxicological profile of enzymes for human health

Enzymes have an excellent safety profile with little ability to cause adverse responses in humans. They are unremarkable for acute toxicity, genotoxicity, sub-acute toxicity and repeated dose toxicity. Reproductive toxicity and carcinogenicity are not endpoints of concern. However, like any other proteins, enzymes act as respiratory sensitisers (1). Respiratory sensitisation due to exposure to enzymes results in the development of IgE antibodies, which are entirely specific to the enzyme in question. Combined exposure to several enzymes will therefore not lead to a synergistic, additive or antagonistic effect (2).

No synergistic effect following exposure to combined substances has been documented in the course of more than 50 years.

The Derived Minimal Effect Level (DMEL) of enzymes

In the 1970s, the American Conference of Governmental Industrial Hygienists (ACGIH) established a Threshold Limit Value (TLV) of 60 ng/m³ for one class of enzymes, subtilisins (3). Since the establishment of this TLV, enzyme and detergent manufacturing industries have carefully and successfully controlled the exposure to enzymes in their production sites (4,5,6,7). Based on 40 years of systematic monitoring of medical and enzyme exposure data from these industries, it was possible in 2010 to establish a DMEL for occupational enzyme exposure to all enzyme classes of 60 ng/m^3 as the medical data showed this exposure level to be sufficiently safe (8).

For consumers and professionals, the DMEL was set to 15 ng/m^3. The DMEL for consumer/professional exposure was set four times lower than that for occupational exposure as risk mitigation relies on product format, formulation and use instructions, as opposed to exposure control and health surveillance (8).

As the DMELs for both occupational exposure and consumer/professional exposure are based on medical and exposure data, **any potential mixture effect is already accounted for**.

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This is supported by data (4,5,6,7) showing that controlling airborne exposure using the DMEL as a target leads to a safe working environment with a very limited number of allergies. Incidents of enzyme allergy have been reported in cases where risk mitigation and the DMEL have not been applied or have failed for technical reasons (9).

Large epidemiological studies of consumers and professionals (10,11) have shown that exposure to mixtures containing enzymes does not result in sensitisation. In one study, clinical data of 15,765 individuals collected in 40 years were examined and it was concluded that exposure to enzymes via consumer use of enzyme containing products does not lead to the development of sensitisation or allergy. Hence, potential additive or synergistic effects from other consumer products does not exist or is of no importance. In another study, 400 patients with pronounced allergy towards common inhalation allergens, food allergens and allergens of bees, wasps or drugs were tested for sensitisation towards 19 different commercial enzymes. None of the patients showed sensitisation towards any of the enzymes, even though they represented a highly susceptible group of individuals.

Amongst respiratory sensitisers registered under REACH, a DMEL is available for 23 substances, all of which are enzymes.

As stated in the DMEL workshop background document (12), respiratory sensitisation is considered to be a non-threshold effect and, in addition, no validated animal or in vitro methodology is available to evaluate respiratory sensitisation and establish dose-response relationships. Potentially, respiratory sensitisers could make use of DMEL approaches, but the issue is complex and the use of DMELs is likely limited by data-availability. Wood and Rambøll concluded that a DMEL for respiratory sensitisers can potentially be excluded on the basis of technical non-feasibility.

Consequences of introducing a MAF for enzymes

The safety of workers, professionals and consumers has been demonstrated using the established DMELs, which already take any potential mixture effect into account. A MAF factor will therefore not provide a safer environment for either workers, professionals or consumers.

According to the European Commission's approach for introducing a MAF, as presented at CARACAL 48[1], respiratory sensitisers will be exempted from implementing a MAF factor because, in general, dose-response cannot be established for this group of substances, as also reported by the Wood and Rambøll background document. However, in case a DMEL has been established for a respiratory sensitiser, the MAF will have to be implemented. It seems completely unjustified that the enzyme industry, which has systematically and carefully worked to control exposures for over 50 years and, based on this, has established a DMEL that will provide a safe environment, including potential effects from mixtures, will now have to implement a MAF, whereas other industries that have not focused on establishing a DMEL will not have this obligation.

[1] CARACAL-48 (28 March 2023) AP 4.1

Further, the present proposal for introducing a MAF holds a tonnage limit so that only substances with more than 1000 t/y will have to implement a MAF of 5. The DMEL of either 60 ng/m^3 or 15 ng/m^3 established for enzymes covers all enzyme classes. However, some enzyme classes will be above the 1000 t/y, whereas others will be below. This means that although the potential risk is the same for all enzyme classes, some classes will have a DMEL of 60 ng/m^3 or 15 ng/m^3 and other classes will have a DMEL of 12 ng/m^3 or 3 ng/m^3 because of MAF. This is not scientifically justified, and it will be extremely confusing for the downstream users of enzymes.

Conclusion

- The only toxicological endpoint that *could* be of concern is the intrinsic potential of enzymes – like all other proteins – to act as respiratory sensitisers, in which instance a MAF would not be appropriate as an allergenic response is specific only to the allergen in question. No additive or synergistic effects towards other enzymes or other substances have been demonstrated and, should any exist, they would be included in the DMEL as it was derived from real-world human data in co-exposure situations.

- It is unjustified that a MAF of 5 will have to be implemented for enzymes because this industry, through decades of thorough and systematic work, has been able to establish a DMEL, whereas other respiratory sensitisers are exempted from MAF because of no established DMEL.

- A MAF of 5 implemented for some specific classes of enzymes but not others will not be scientifically justified and it will be extremely confusing for the downstream users of enzymes.

- A MAF would ignore the 50 years of industry experience in managing enzymes safely and effectively for workers, consumers and professionals.

Enzymes at-a-glance

Enzymes are a special class of proteins produced by fermentation. They are required by all living organisms, including humans, to conduct the physiological processes essential for growth and life. They act as catalysts that speed up the rate of specific chemical reactions and are used to make and improve nearly 400 everyday consumer and commercial products in industries from food and beverages, animal nutrition and textiles through to household cleaning, biofuels and energy generation.

All enzymes are readily biodegradable and hence pose no risk to the environment. They generally exhibit no specific environmental toxicity and are hence not classified for the environment. Industrial enzymes have an excellent safety profile with little ability to cause adverse responses in humans. For detailed information about enzymes and their technical, food and animal feed uses, see About enzymes: definition, how they work and more - AMFEP.

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About AMFEP

AMFEP is a non-profit European industry association created in 1977. AMFEP currently has 30 members, representing over 90% of the European and over 80% of the world enzyme market. AMFEP serves as a hub for information exchange and dialogue between enzymes producers and formulators, industry organisations, the scientific community and policy-makers and promotes co-operation on regulatory and safety aspects of enzymes. For further information about AMFEP, please visit our website.

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