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International Association for Soaps, Detergents and Maintenance Products

A.I.S.E. CASE STUDIES ON THE MAF

Comments for Distribution

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On the 4th of May the European Commission published an inception impact assessment (roadmap) on the revision of REACH prompted by the CSS. One of the key actions proposed under the CSS is the inclusion of a Mixture Assessment Factor as part of Chemical Risk Assessments in REACH to take account of potential combined exposures from chemicals. The proposal of a MAF still has various areas requiring clarification and is a fundamental discussion, considering it's impacts on chemical legislation, on industry but also on the products placed on the market with consequences for end users and society.

The MAF should be science-based and should consider societal, economic, and practical considerations as well as concerns for the risks of potential combined exposures. A proposal for regulatory change to REACH should also carefully consider the current rules of chemical legislation and to what extent the concerns of combined exposure are already being addressed by the current regulatory framework. Ensuring enforcement of current rules may be a more adequate solution in some cases.

In this paper, A.I.S.E., along with the sectors that have participated to drafting this document, namely AMFEP, CLER[1], brings forward some case studies for the MAF. These case studies demonstrate why a MAF should not be applied as a blanket, generic number and needs to be looked at on a case-by-case basis related to criteria like tonnage, hazard profile, biodegradability, mode of exposure, mode of action for each substance, the level of understanding of the potential toxicity, solubility etc. to assess the real risk of combined exposure (more data = more refined RA possible)

The concept of using a blanket MAF value has in fact also been criticised by authority representatives. As stated in the article recently published by the German BfR called "The EU chemicals strategy for sustainability questions regulatory toxicology as we know it: is it all rooted in sound scientific evidence?"[2] the occurrence of combination effects should not be a default assumption, unless there are data supporting such mechanisms to be potentially relevant. As an alternative to a generic MAF, the EFSA "Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals"[3], proposes to use tiering principles and Margins of Exposure (MoEs) instead of a blanket value. This paper further expands on alternatives in the last chapter.

The lack of solid scientific evidence for a blanket MAF is further acerbated by the possible negative effects, such as driving of additional, unnecessary risk management measures to products or to mitigate sustainable uses of products like washing at low temperatures or compaction of packages. It will also increase animal testing/data generation for companies that will need to refine risk assessments in order to derive higher safety margins and reverse the

[1] AMFEP Association of Manufacturers and Formulators of Enzyme Products
CLER Council for LAB/LAS www.CLER.com
[2]Doi: https://dx.doi.org/10.1007%2Fs00204-021-03091-3
[3] Doi: https://doi.org/10.2903/j.efsa.2019.5634

impact of an arbitrary and unscientific MAF. Such additional testing while having no demonstratable benefit to human or environment health will increase costs and more importantly should be avoided from animal welfare point of view.

More details on the impacts of the MAF for our industry are outlined in the following case studies presented. The case studies should be considered examples of key concepts, rather than comments on the specific substance or use.

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Surfactant Example - LAS

Surfactants are key ingredients in detergent and maintenance products. They act by changing the surface tension of water to assist cleansing, wetting surfaces, foaming, and emulsifying, to remove particles of dirt and soil.

Linear alkylbenzene sulphonate (LAS, CAS No. 68411-30-3) is an anionic surfactant. It was introduced in 1964 as the readily biodegradable replacement for highly branched alkylbenzene sulphonates (ABS). Since it is introduction, LAS has become the most widely used surfactant in laundry detergents and cleaning products worldwide. LAS is often the main surfactant used because of its unsurpassed cleaning properties. In modern detergents and cleaning products, a mixture of surfactants, typically including LAS, are used along with other ingredients such as enzymes (see next section) to optimize cleaning performance.

The environmental and human risk assessment of LAS published by HERA in 2013 estimated a total consumption tonnage of about 430 kt for the year 2005, with a breakdown by household applications of about 350 k, corresponding to more than 80% of the total according to an independent survey of A.I.S.E. companies.

In addition, surfactants do not lend themselves to combined exposures following release into the environment due to the Detergent Regulation (EC) 648/2004 biodegradability requirements. In general, we question the relevance of a blanket MAF on surfactants.

Why a blanket MAF is not scientifically reasonable for LAS:

As the MAF is an indicator of excess mixture risk i.e. risk of a mixture after successful risk management of all individual compounds, there is evidence for why such a risk is not relevant for LAS:

For Environment:

- The literature shows that mixture toxicity is dominated by a few key chemicals of high concern. e.g. pesticides and/or pharmaceuticals. (Diamond et al., 2018). LAS has a nonspecific mode of action described as “narcosis toxicity” (Roberts 1991; Fendinger *et al.,* 1994). Literature shows that chemicals of high concern dominate any potential mixture toxicity concern and these do not include substances with narcosis toxicity. Investigations were done in the past (QSAR’s) to understand the combined affected of unintended mixture of anionic surfactants and it was shown that combined exposure to similar types of anionic surfactants is not resulting in unacceptable risks to the environment (McDonough et al. 2016). The results of these studies indicate there is a significant margin of safety for LAS and the entire class of anionic surfactants.
- The results of a recent eco-epidemiology study in Germany (Holmes *et al.,* 2021a; Holmes *et al.,* 2021b) compared ecological water quality, including algae, fish, macroinvertebrates and macrophytes, at 3970 river and stream positions with the predicted surfactant concentration at those sites. No correlation was found between ecological status and the surfactant concentration, suggesting that the surfactant concentration or any potentially harmful mixtures containing surfactants is not driving the ecological status.
- The introduction of the EU Detergents Regulation (EC) 648/2004 in October 2005 made ultimate biodegradation obligatory throughout the EU for all groups of surfactants used in

domestic detergents[4]. As a consequence, a surfactant is less likely to contribute to combined exposure in the environment once the ingredient is released down the drain. This is because, while results of screening tests on biodegradability are one input factor in the risk assessment modelling in EUSES, a MAF of 10 placed on the current RCR's would result in an unsafe use. Conversely, combined exposure is not deemed relevant for this chemistry due to the biodegradability.

- LAS has a high removal rate in STP (absorbing to solids) that is also lowering the amount of LAS that will be available to contribute to mixture toxicity after STP in the aquatic compartment. Any LAS in the sludge will be quickly degraded.

For human health:

- Potential health hazards of LAS have been well characterized to include systemic endpoints such as; oral, inhalation and dermal endpoints (ECHA, 2021 (Registration Dossier - ECHA (europa.eu)). ECHA, 2021 derived a Derived No Effect-Level (DNEL) value of 0.425 mg/kg bw/day for LAS based on a repeated dose sub-chronic oral toxicity study (with Wistar JCL Rats (Male/female)), resulting in an No Observed Adverse Effect Level (NOAEL) of 85 mg/kg bw/day based on systemic effects. Considering this substance will not be used in products where oral exposure is anticipated (via ingestion), there are no combined exposure effects anticipated where LAS products are concerned (ECHA, 2021). Furthermore, extensive toxicological assessments are carried out on all products to ensure the LAS products' formulations are meeting regulation acceptance requirements where all human health endpoints are concerned (ECHA, 2021 (ECHA registration dossier)).

Blanket MAF on LAS and the resulting impacts:

For this chapter, A.I.S.E. evaluated the impact of a blanket MAF for this key ingredient in the professional and consumer use sector for detergents and maintenance products. Human health (HH) and environment (ENV) were both considered.

Based on the most recent Chemical Safety Assessment from the LAS suppliers, a MAF of 10 would cause the assessment to conclude an unacceptable risk for the environment for several uses of LAS in professional products. In the current consumer CSR, the exposure scenario covers an extremely conservative unrealistic situation where a consumer uses all types of product that may contain LAS within one day. Based on the current CSR, a MAF of 10 will result in unacceptable risk (RCR >1) for consumer safety.

In the cases of performing an assessment with a different (higher tier) modelling tool would not lead to a different outcome, nor would introducing additional risk management measures (RMM) be possible in practice. Lowering concentration would impact product effectiveness. Hence, these products would not be safe for use and would have to be removed from the market.

Considering formulations holistically, versus focussing on specific ingredients is crucial. LAS is a crucial ingredient in formulation for other benefits like water saving, heat/energy saving or compaction (i.e. concentrated products that use less water and packaging) to be achieved.

[4]https://www.aise.eu/our-activities/regulatory-context/detergents/biodegradation-of-surfactants.aspx

Conclusion:

The scientific evidence does not support the application of a blanket MAF for human health or environmental exposure. In addition, such a value has impacts on product effectiveness, issues with overburdening end-users by applying additional or unrealistic RMMs or practical issues with implementation of higher tier tools or measuring actual exposures and ensuing costs with the generation of data. As there are no way to readily reduce RCR for some of those uses, the application of MAF of 10 may result in removal of detergents containing LAS from the market, although LAS is not easily replaceable. Considering formulations holistically, versus focussing on specific ingredients is crucial to allow for other benefits like water saving, heat/energy saving or compaction (i.e. concentrated products that use less water and packaging) to be achieved. While the consequence is huge, such actions will not contribute to higher human or environmental safety, and in practice can conflict with sustainability or regulatory objectives (e.g. OSH and unnecessary use of PPE).

The example of LAS clearly indicates why a MAF value should be considered on a case-by-case basis, taking science into account, mode of action, sustainability, and socio-economic considerations.

Enzymes

Enzymes are catalysts that increase the rate of chemical reactions occurring in a variety of biological processes including digestion and growth. In the detergent industry, commercial enzymes are used to provide a higher degree of stain removal, whiteness, fabric and colour care and overall cleaning performance. These ingredients are selected based on performance and the use that is required. Enzymes are used in various cleaning applications - these highly targeted biocatalysts help effectively eliminate stains by making them more easily removed by surfactants (A.I.S.E. *et al.,* 2021, Enzyme factsheet). In 2002 according to the enzyme producing companies ca. 950 tons of protease, 150 tons of amylase, 15 tons of cellulase and 8 tons of lipase was produced in the EU for the EU detergent market (HERA project 2005). For more up to date information, the REACH dossiers cite the following tonnage values: protease (>1000), amylase (>1000),cellulase (>1000),lipase (>1000).

Finally, for an estimate of the economic impact of reducing the use of these ingredients, we outline below three key sectors where Enzymes are used, and the market value for the product category.

Product Category of Enzyme Use (Ref. cleanright.eu, expert input)	Market Value of Product Category (Ref. A.I.S.E. 2021)
Consumer Laundry Care	15.3 billion Euro
Consumer Automatic Dishwash	3.2 billion Euro
Professional Laundry	0.5 billion Euro

Why a blanket MAF is not scientifically reasonable for Enzymes:

Industrial enzymes have an excellent safety profile, with little ability to cause adverse responses in humans. Enzymes do not pose concerns of acute toxicity, repeated dose toxicity, genotoxicity, carcinogenicity, or reproductive/developmental toxicity.

The toxicological endpoint of concern associated with exposure to enzymes, like to any other proteins, is that of respiratory sensitisation. If exposed by inhalation to a sufficiently high dosage of airborne enzyme, an individual may become sensitized. Sensitisation is an indicator that an individual has been exposed by inhalation at some point in time to a high dosage of the specific sensitizer. For enzymes it is known from occupational industrial settings that up to 10% of the exposed population may become sensitized to an enzyme during their work life (Basketter *et al.,* 2015).

If a sensitized individual is further exposed to high airborne concentrations of the same enzyme then they may develop allergy symptoms, which in the beginning will be mild symptoms like sneezing or watery eyes, but which in case of continued exposure to that enzyme may develop into more severe symptoms like asthma. For enzymes it has been shown that approx. 1% of the occupationally exposed population in the detergent manufacturing industry may develop allergy symptoms during their work life (Basketter *et al.*, 2015). Becoming allergic to an enzyme is therefore a two-step process, in which the first step is sensitisation and next step is allergy. No allergy arises without the sensitisation step, and as it appears that sensitisation requires lower

dosage than the development of allergy (Basketter *et al.,* 2012) controlling exposure to protect against sensitisation will also protect against subsequent allergy.

It is important to mention that the nature of any allergic response is entirely specific to the allergen in question. It occurs only when the immune system encounters the specific allergen to which the subject is sensitized. It is independent of whether there is simultaneous exposure to other substances, including other allergens. **For this reason, application of a MAF to help control the potential health risk derived from exposure to enzymes is inappropriate.**

For environment, enzymes released after laundry wash, are biodegraded in wastewater treatment systems, and therefore pose no risk to fauna and flora in the environment, or indeed to human health. The same is true for unintended release into freshwater systems as natural biodegradation processes can readily, and quickly, cope with these proteins. Their inherent safety in these ecosystems is a clear advantage to their function.

The Risk Management of Enzymes:

For Enzymes, DMEL's (Derived Minimal Effect Levels) were established in 2009[5] instead of DNEL's (Derived No Effect Levels) for occupational and for consumer exposure, respectively, (Basketter *et al.,* 2010). This was because, as in common with many sensitising materials, there is no documented dose response relationship for these ingredients.

For occupational exposure, the experience of the detergent industry over the last 50 years has allowed the establishment of DMELs that account for the mixture (formulation) in which the enzymes are presented, and thereby minimise risk of sensitisation as well as preventing the elicitation of allergy symptoms (Basketter *et al.,* 2021). This data is based on epidemiological studies that report on the sensitisation of workers that are exposed to a mixture of enzymes and other co-formulants at the workplace.

The occupational DMEL for enzymes have shown to be very effective in controlling exposure to enzymes and thereby protecting workers against allergy to enzymes. Only in cases where risk mitigation and the DMEL have not been applied, or have failed through technical reasons, have incidents of enzyme allergy been reported (Cullinan *et al.,* 2000). As the occupational DMEL has shown its efficiency in manufacturing settings in the presence of other formulation substances, it is considered to provide the necessary protection regarding mixtures covering potential synergistic effect of other chemicals. Therefore, the current DMEL's for enzymes are entirely appropriate and do not require the application of a MAF.

Meanwhile, the DMEL for consumer and professional exposure has been set 4 times lower than the DMEL for occupational exposure as risk mitigation relies predominantly on product format, formulation and use instructions. Instead of engineering exposure controls personal protective equipment and health surveillance are generally not considered for such uses and it is also not feasible to consider such risk management measures to compensate for a MAF (Basketter *et al*., 2010).

Allergy to enzymes among consumers of enzyme containing laundry and cleaning products has not been reported since the late 1960's. At this time encapsulation of the enzymes along with

[5] The occupational DMEL for enzymes have been established based on; the Threshold Limit Value (TLV) established for Subtilisin of 60 ng/m3 (ACGHIC 2011), 50 yrs. of studies, data, exposure modelling and exposure measurements, product stewardship programs for enzymes which are key in safe manufacturing and safe use by consumers of enzyme containing detergent products

other formula changes were made to ensure that consumer exposure levels were sufficiently low and the likelihood of either the induction of sensitisation or the elicitation of clinical allergy symptoms would be highly improbable.

In a study in 2010 (Sarlo *et al.,* 2010), clinical data from a range of sources collected over a period of 40 years were analysed. These include data from peer reviewed literature and enzyme specific sensitisation tests among detergent manufacturers' employees and from clinical study subjects. In total, enzyme specific sensitisation data were available on 15,765 individuals. The clinical testing revealed that the prevalence of enzyme specific sensitisation in the population is very rare (0.126% since 1977). This demonstrates that exposure to enzymes via consumer products that frequently contain several different enzymes and other co-formulants use of enzyme containing products does not lead to the development of sensitisation and allergy, and therefore that any potential adjuvant effect from various consumer products does not exist or is of no importance.

These data confirm that the risk to consumers has been properly assessed and managed, and that the DMEL set for consumer exposure to enzymes is appropriate.

For some ingredients the established exposure limits [DNEL's, DMEL's, etc] already factor in the effect of other ingredients with which those products are formulated. When considering exposure of any workforce to hazardous agents it is the duty of an employer to consider any synergistic effects between the materials that are being handled. This is the case of the DMEL for enzymes as we described in the previous section. Additionally, exposure limits are already exceptionally low, and generally exposure and risk assessment rely on air monitoring data. The introduction of a MAF would make such measurements in many cases impossible due to the limit of detection of the – already highly specialised – available analytical methods.

This contributes to the evidence that a blanket MAF, that does not consider the modes of actions and already existent regulatory framework, is not suitable for these ingredients.

Blanket MAF on Enzymes and the resulting impacts:

The application of a MAF on enzymes being a case in point of this document, will drive exposure limits so low as to make those limits unattainable in addition to unmeasurable. The impact of doing this would prevent those ingredients from being utilised, and the benefits of those ingredients denied to the end users.

There are no alternatives to enzymes, in fact enzymes are already used as alternatives to other ingredients. If enzymes were banned this could result in more use of surfactants and a need to use higher washing temperatures which heavily impact the level of sustainability of the washing cycle. Enzymes provided the alternative technology to transition away from phosphates and phosphonates which are now restricted in consumer detergents.

Preventing or reducing the use of enzymes would be a retrograde step given their environmental profile, the reduction in harsh corrosive chemicals that they achieve, and the reduction in energy used allowing low temperature washing. The application of a MAF must consider how an exposure limit has already been set before application.

Conclusion:

The implementation of a blanket MAF for enzyme ingredients does not make sense from a scientific point of view, as there is no documented dose response relationship, and the limit value

has been supported by epidemiological study that already consider exposure to mixtures and (3) the increased energy consumption in case enzymes must be phased out of detergent products. In addition, the only toxicological endpoint of concern associated with enzymes is that of respiratory sensitisation. A MAF would not be appropriate as allergenic response is specific to the allergen in question.

The current DMEL for occupational exposure provides adequate protection of workers, as incidents of allergy to enzymes have only been reported when this DMEL has not been complied with. For consumers no incidents of allergy to enzymes using consumer laundry products have been reported since the late 1960's, even if the amount and variety of enzymes have increased since then. Data shows that the DMEL for consumers provides adequate protection. Based on the above, sufficient protection of humans and environment has already been established.

Implementation of a blanket MAF would thus contrast with the science, it would not consider the long-standing, demonstrated, 50 years of experience of industry in effectively managing these ingredients, and finally may prevent the use of these ingredients in important applications. In the case of enzymes this would be a retrograde step given their environmental profile, the reduction in harsh corrosive chemicals that they achieve, and the reduction in energy used allowing low temperature washing.

The application of a MAF is thus not appropriate for Enzymes.

Preservatives

Water-based liquid detergents need a method of preservation, without this they would be contaminated by micro-organisms and result in product going to waste. Preservatives thus play a fundamental role to prevent product damage. They ensure durable shelf and storage life, thereby reducing product losses, and eventually, support sustainability by optimising use of resources.

These ingredients are added in the smallest effective quantity to protect products from spoilage; however, a certain quantity still needs to be added as below a certain concentration, an ingredient will no longer have preservation function.

These ingredients are primarily used in consumer water-based products, rather than professional products which can avail of other techniques. They are found in circa. 60% of the total household market and about 13% of the professional cleaning sector. For consumers, the current market trend – in line with consumer choices – shows an increasing preference for liquid formats. These products also enable compaction and sustainability savings as liquid formats can be produced in a less energy intensive way (A.I.S.E. Preservatives Factsheet 2018).

Why a blanket MAF is not scientifically reasonable for Preservatives:

Example of important preservatives in the Detergent sector are:

- Glutaraldehyde (Glutaral)
- Benzisothiazolinone (BIT)
- Methylisothiazolinone (MIT)
- Methylchloroisothiazolinone/ Methylisothiazolinone 3:1 (CIT/MIT 3:1)
- Octylisothiazolinone (OIT)
- 3-Iodo-2-PropynylButylCarbamate (IPBC)
- DMDM Hydantoin (DMDMH)

For these preservatives when used in consumer water-based products the hazard endpoint is skin sensitisation.

Skin sensitisation is the first step in the development of a skin allergy in which following epicutaneous application of a substance the skin is prone to a T-cell mediated immunological response specific for the substance. This is the induction phase where the sensitising chemical penetrates the epidermis and binds to skin proteins/peptides to create an immunogenic complex. This complex activates antigen presenting cells which triggers the production of T-cells. The second step, the elicitation phase, occurs upon a subsequent exposure to the sensitizer and results in a clinical response. Induction and elicitation are both threshold effects, and usually elicitation is lower than induction. Skin sensitisation induction is chemical specific. For elicitation, it is acknowledged that there could be some cross reactivity, however, targeting this through REACH is not appropriate as REACH risk assessments are based on induction.

If we consider an example where a person is exposed to both Methylisothiazolinone (MIT) and Benzisothiazolinone (BIT), generally it is agreed that the induction thresholds will not be affected and there is no need to consider any cumulative effect due to the specific immune reaction being related specifically to one allergen.

In another example: a person is exposed to one skin sensitizer from a shampoo, and the same sensitizer from a detergent. What drives skin sensitisation is the dose/ unit area of skin exposed. That would be coming from various products only if these were used, on the same skin surface area, closely together in time. However, in practice this is unlikely as i) the potential residues of preservatives on clothes following use of detergents are normally negligible ii) household and cosmetic products not always share the same set of preservatives, hence accumulation is unlikely iii) people normally rinse their hands when using different products

Current practices for risk assessment of sensitizers, and local effects in general, are already different compared to systemic toxicity. Dose/concentration addition is typically used as a first-tier approach to mixture toxicity. For sensitizers this approach is less suitable because the dose per unit area is important. Thus, while adding an assessment factor (AF) to a NOAEL to derive a DNEL for systemic effects is possible, for local effects the derivation of cut-off values is done differently (Api *et al.,* (2020) and Kienhuis *et al.* (2015)). Other approaches should be developed to take mixture effects for local effects.

The alternative to a blanket MAF would be to use refined concepts and targeted risk assessment approaches for substances with known properties related to combination effects. Regarding the impact of the formulation on the induction threshold of a skin sensitizer, as part of the assessment of the Biocidal Products Regulation (EU) 528/2012 a mixture assessment is already carried out. The BPR mixture assessment aims to provide a product/formulation risk assessment (BPR Annex III Art 8).

The Biocide Regulation:

- Aims to provide a product/formulation risk assessment. Considering a limited number of coformulants and fixed individual fractions of each coformulant
- It allows however possibilities for Risk assessment refinements: Tiered approach, Data production (tox, ecotox, ..) on individual substance/whole product, additional RMM

The BPR provides a highly complex framework to assess preservatives and the addition of further requirements seems disproportionate for these ingredients.

Blanket MAF on Preservatives and the resulting impacts:

The application of a MAF to these types of ingredients, preservatives being used as an example in this document, will drive exposure limits so low as to make those limits unattainable in addition to unmeasurable. The impact of doing this would prevent those ingredients from being utilised, and the benefits of those ingredients denied to the end users.

Preservatives are already added to the smallest quantities to be effective. They are necessary ingredients as water-based liquid products need a method of preservation to waste, allow longer term shelf and storage life, and support sustainability by optimising use of resources.

With regards to using alternative ingredients to the approved preservatives that have the main hazard of dermal sensitisation, there are some fundamental issues. The majority of the current list of Active Substances available under BPR PT6 can actually not be used by the detergent industry for various reason: including technical limitations like surfactant incompatibility, or toxicological restrictions (A.I.S.E. Preservatives Factsheet 2018). In conclusion the resulting

impact would be significant, as various ingredients may be further limited from use and there would be issues in finding alternatives.

Conclusions:

In this example we bring forward preservatives. For these preservatives when used in consumer water-based products the relevant hazard endpoint is dermal sensitisation.

Skin sensitisation induction is chemical specific. For elicitation, it is acknowledged that there could be some cross reactivity, however, targeting this through REACH is not appropriate as REACH risk assessments are based on induction. Other approaches should be developed to take mixture effects for local effects. The alternative to a blanket MAF would be to use refined concepts and targeted risk assessment approaches for substances with known properties related to combination effects.

However, the application of a MAF would drive exposure limits so low as to make those limits unattainable in addition to unmeasurable. Preservatives are needed to prevent microbial contamination and products going to waste. Furthermore, alternatives to key ingredients used in the sector are not always available.

NaOH

Sodium Hydroxide is a crucial functional ingredient in products like drain cleaners and oven cleaners for both professional and consumer use.

NaOH must be used at certain concentrations in oven and drain cleaners for it to be effective. At such concentrations it will result in a product that is classified and require hand and eye protection, thus the endpoint to consider is the respiratory endpoint.

It has a vital role is various applications in varying concentrations based on the end of use the product. It is crucial to note that the concentration of sodium hydroxide has a correlation with product effectiveness.

- High alkali (NaOH) liquids which are effective in blockages in the kitchen, where food residue is the primary blockage.
- Lower alkali (NaOH) products are instead formulated with bleach and lower NaOH concentration and are more effective in application like bathroom drains where the presence of hair is the key issue and thus the bleach facilitates this by dissolving the hair blockage.
- There are applications that are more in the drain caring option and need to be used more frequently. These would have an even lower alkali dose and may have higher density to move slower in the drain and interact more slowly with problem zones of blockage. These might need more frequent use.
- Sodium hydroxide-based oven cleaners help convert fats and grease to a form that dissolves in water. It is a heavy-duty degreaser. The concentration of sodium hydroxide is specific to the produce use.
- Sodium hydroxide also works as a sterilizer for specific industries. Professional cleaners use sodium hydroxide in clinical areas to destroy 99.9% of bacteria in that area for it to be classed as a sterile surface before using again.

Why a blanket MAF is not scientifically reasonable for NaOH:

For Environment:

NaOH does not have any key environmental hazards. Total releases to the environment from all exposure scenarios are not relevant for NaOH due to the following reasons:

- Consumer use of NaOH will be neutralized quickly in the sewer, well before reaching a WWTP or surface water. Even after an accidental release the substance will be neutralised and therefore exposure (including human exposure) to sodium hydroxide via the environment is expected to be negligible[6].
- For the environmental risk assessment on which the original CSR was based the focus is on the aquatic environment, as the emissions of NaOH in the different life-cycle stages (production and use) mainly apply to (waste) water.

[6] https://publications.jrc.ec.europa.eu/repository/handle/JRC41906

- The aquatic risk assessment in turn deals with the effect on organisms/ecosystems due to possible pH changes related to OH- discharges, as the toxicity of the Na+ ion is expected to be insignificant compared to the (potential) pH effect. Only the local scale (thus not the regional scale) is addressed, when applicable including sewage treatment plants (STPs) or waste-water treatment plants (WWTPs), both for production and industrial use.
- Production and use of sodium hydroxide are normally not expected to increase the pH of the environment. Even after an accidental release the substance will be neutralised and therefore the human exposure to sodium hydroxide via the environment is expected to be negligible. Therefore, no direct or systemic exposure is expected from sodium hydroxide via the environment.
- For production: based results cited in a questionnaire among users (EU Risk and original CSR assessment), it is concluded that discharges of NaOH from production to STPs/WWTPs and receiving waters are well controlled in all investigated cases. Considering the existing EU Directives for pH control for surface water and the data of many Member States on (additional) national regulations to control the pH of waste waters (STP influents) and surface waters it is concluded that STPs and surface waters are sufficiently protected regarding pH changes.
- Use: other results also cited in a questionnaire among users (EU Risk and original CSR assessment) indicate that in most cases the final effluent did not contain NaOH anymore, so it is concluded that discharges of NaOH from the various downstream applications rarely occur. If discharges do occur, they are well controlled in all investigated cases and are often covered by EU and/or national regulations.

For human health:

For the EU human health risk assessment, the focus on the risks were from acute exposure (local effects, thus not systemic effects), both for workers and consumers. Thus, the hazard endpoint would be respiratory irritation. Irritation requires a qualitative risk assessment (for PPE, respiratory protection) and a quantitative risk assessment for irritation may not be appropriate to for these hazards.

Why are local effect the focus?

For the use of sodium hydroxide in oven cleaners or drain cleaners/openers, the sodium hydroxide would be the key ingredient of the formulation. It is not the practice for such formulations to contain other ingredients that will contribute to local effects. Thus, combination effects are not realistic in the formulation.

Following release these are also not realistic. The local (corrosive) effect of the substance combined with rapid neutralisation in waste-water treatment mean that some of the more ‘complex’ exposure assessments were deemed unnecessary. In reality, a combination effect for NaOH is unlikely, unless a person is performing multiple activities (drain cleaning and oven cleaning) at exactly the same time.

Blanket MAF on NaOH and the resulting impacts:

Based on the most recent Chemical Safety Assessment from the NaOH suppliers, a MAF of 10 for professional use of drain cleaners and oven spray cleaners would result in the use not being considered safe. Introducing additional risk management measures (RMM) would not be possible in practice or would go against OSH objectives.

For consumer use, adding a MAF = 10 would also not make the use safe and adding of RMMs or performing an assessment with a different (higher tier) modelling tool would not be a possibility.

Reducing the concentration of sodium hydroxide would reduce the effectiveness of the final product. Especially high alkali drain cleaners, such as those used in kitchen applications, could no longer be deemed as safe to place on the market. Thus, consumers would need to default to products with lower Sodium Hydroxide concentration, which would be less effective depending on the final application.

The consequence of less effective products would range from needing greater quantities of product to achieve the result (with consequence on sustainability), or the need to move to alternative products which could result in different risks to those of sodium hydroxide based products.

Applying a non-scientific MAF would be considered inappropriate because it would ultimately affect our ability to formulate products that affectively provide customer benefits such as degreasing and disinfection.

In addition, it is important to note that special care is taken into consideration regarding sodium hydroxide contained products (due to their corrosive nature) to develop a conservative and informative product use labels. Thus, consumers are already being informed on how to use these products safely.

Conclusions

We thus present the example of sodium hydroxide to bring forward an additional case where there would be no scientific evidence to support the need for a blanket MAF to consider combined exposure. Meanwhile, the inclusion of such a blanket MAF would result in impacts on the products that would be made available on the market to support needs of consumers in the cleaning and maintenance of drain cleaners and over cleaners. Inclusion of a MAF, which would oblige companies to reduce the concentrations being used for this ingredient, would result in less effective products or the elimination of product categories being placed on the market.

Conclusion:

Thus, these case studies have been presented to illustrate:

- That a blanket MAF is not always appropriate considering the science
- That there are key socioeconomic and practical consequences to applying a blanket MAF on ingredients for downstream users, consumers and the products to be placed on the market.
- Our proposal is for ingredients to be looked at on case-by-case basis related to the Mode of Action for each substance and the level of understanding of the potential toxicity (more data = more refined RA possible).

Alternatives to a blanket MAF

Based on our analysis in the chapter above, we conclude that a blanket MAF will not be an appropriate tool for assessing combined exposures. A science based; case-by-case approach would be a more suitable solution. In addition, the importance of enforcement of current rules must be mentioned and the fact that REACH does not cover all combinations of chemicals in the environment.

Considering however the value for case by case approaches we share some alternative solutions.

1. Paper in Nature: Tralau et al. propose to proactively investigate the likelyhood of co-exposure and its potential effects for possible mixtures and their single substances using an adapted concept of the exposome and large-scale hazard screens. The concept foresees that only mixtures flagged as having potential risks using this concept should be considered for further regulatory action e.g. the adaptation of specific safety factors or the application of risk mitigation measures (Traulau *et al.,* 2021)

2. Aquatic toxicity of mixtures of surfactants can be accurately calculated based on their QSAR properties and additivity of mixtures (McDonough *et al.,* 2016).

3. EFSA "Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals"[7], proposes to use tiering principles and Margins of Exposure (MoEs) instead of a blanket value

4. For Environment a proposal could be **using ECHA tonnage info with information on mode of action for assessments.**

   To address the risks of unintended mixtures in the environment. We would propose that the assessment should not be made by individual registrants, but centrally, e.g. by ECHA themselves or a scientific body on their behalf. Work by Posthuma *et al.*, (2019) detail scientifically appropriate methods to assess the risks of mixtures, including approaches such as the summation of toxic units, risk quotients or mixture toxic pressure.

   During the REACH registration process, registrants provide volume information for their usage of a substance, with percentages split and allocated between uses and associated exposure scenarios, predicting the resulting concentrations in the environment. In addition to this information, ECHA has access to the hazard endpoint values submitted as part of the registration dossiers. A toxic unit approach could be taken across all the submitted dossiers.

   As a result of this information, ECHA can calculate the combined mixture toxicity of all registered substances, at least as per the exposure scenarios presented in EUSES. Using this approach, it would be possible to identify substances that are the largest contributors to toxic unit load to each environmental compartment. To go one step further, as suggested by Posthuma *et al.*, (2019), mode of action information could be incorporated. This would be a new information requirement for registrants, however, new modelling approaches exist

[7] Doi: https://doi.org/10.2903/j.efsa.2019.5634

allowing more detailed predictions of mode of action than were previously available and these approaches could be suggested as the default information requirements, as opposed to testing ((Bauer *et al.,* (2018), Bauer *et al.,* (2021)).

The benefits of this approach are that it is more scientifically meaningful, makes use of existing information provided by registrants, and will therefore have significantly less impact when compared to a blanket MAF. The only new information that would need to be elucidated by registrants would be information on mode of action.

Unlike the blanket MAF approach, ECHA will have a scientifically justified pathway to act and work with industry on chemicals that make the highest toxic unit contribution, working together to identify substances that should be the focus for improving safer and more sustainable use of chemicals.

5. Consider criteria to identify specific substances where an additional assessment to consider combined exposure may be considered. This should consider also criteria for exclusion. In addition, the creation of new data should allow values to be refined.
   For example the combination of the following substance criteria could be considered as being important in determining the probability of being a significant contributor to combined exposure risks:
   - Tonnage: the tonnage band in which the substance is registered;
   - Hazard profile: the hazard classification and mode of action;
   - Biodegradability and solubility: the biodegradability and solubility determine the chances of a substance reaching and remaining in an unintended mixture;
   - Occurrence in nature: substances or their breakdown products that are naturally occurring.

   These criteria in and of themselves do not give an indication as to whether they actually cause additional risks in unintended mixtures. However, the combination of these provide valuable information on the chances of being involved in an unintended mixture, and (based on their hazard profile) the chances of contributing to the potential risks of a combined exposure to that unintended mixture.

These are points of thought to discuss further for alternatives to a blanket MAF.

References:

General

Herzler, M., Marx-Stoelting, P., Pirow, R. et al. The "EU chemicals strategy for sustainability" questions regulatory toxicology as we know it: is it all rooted in sound scientific evidence?. Arch Toxicol 95, 2589–2601 (2021). https://doi.org/10.1007/s00204-021-03091-3

EFSA Scientific Committee, More, SJ, Bampidis, et. al. C, 2019. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 2019;17(3):5634, 77 pp. https://doi.org/10.2903/j.efsa.2019.5634

Tralau, T., Oelgeschläger, M, Kugler, J., et al. A prospective whole-mixture approach to assess risk of the food and chemical exposome. Nature Food Vol 2, 463-468 (2021)

For LAS chapter

Diamond et al., 2018. Use of Prospective and Retrospective Risk Assessment Methods That Simplify Chemical Mixtures Associated With Treated Domestic Wastewater Discharges. ET&C37: 690-702

Dyer SD, Belanger SE 2020. Commentary: An amplified address to criticisms and deficiencies found in a recent environmental assessment of LAS. CLER Rev. 17:6-20; available at: https://cler.com/portfolio/vol-17/.

ECHA LAS registration dossier: https://echa.europa.eu/registration-dossier/-/registered-dossier/15879/7/6/2

Fendinger NJ, Versteeg DJ, Weeg E, Dyer SD, Rapaport RA. 1994. Environmental behavior and Fate of anionic surfactants. In: Baker LA (ed), Environmental Chemistry of Lakes and Reservoirs, ACS Advances in Chemistry Series No. 237. American Chemical Society, Washington, DC, p 528.

Freeling et. al, Explaining the rationale behind the risk assessment of surfactants by Freeling et al. (2019), Science of The Total Environment, Volume 721, 2020,136828, ISSN 0048-9697, https://doi.org/10.1016/j.scitotenv.2020.136828.

HERA Project. 2013. LAS. Linear Alkylbenzene Sulphonate (CAS No. 68411-30-3) Human and Environmental Risk Assessment on ingredients of Household Cleaning Products. Revised HERA Report, April 2013; https://www.heraproject.com/files/HERA-LAS%20revised%20April%202013%20Final1.pdf

Holmes CM, Maltby L, Sweeney P, Thorbek P, Otte JC, Marshall, S. 2021a. Increasing Ecological Relevance of Chemical Risk Assessments using Geospatial Approaches: Results from Two Case Studies. SETAC Europe Meeting 2021, Platform presentation 4.05.10; abstract available: https://www.ecetoc.org/taskforce/geospatial-approaches-increasing-ecological-relevance-chemical-risk-assessments/

Holmes CM, Marshall, S., Otte JC, Sweeney P, Thorbek P. 2021b. Surfactant case study: Increasing the ecological relevance of chemical risk assessments using geospatial approaches. SETAC Europe 31st Annual Meeting, Poster presentation 4.05.09; abstract available:

https://www.ecetoc.org/taskforce/geospatial-approaches-increasing-ecological-relevance-chemical-risk-assessments/

McDonough K, Casteel K, Itrich N, Menzies J, Belanger S, Wehmeyer K, Federle T. 2016. Evaluation of anionic surfactant concentrations in US effluents and probabilistic determination of their combined ecological risk in mixing zones. Sci Total Environ 572:434–441.

Roberts D. 1991. QSAR issues in aquatic toxicity of surfactants. Sci Total Environ 109/110: 557-568.

Scott D. Dyer, Drew C. McAvoy, Scott E. Belanger, John Heinze, Ricky Stackhouse, Hans Sanderson, Donald J. Versteeg, Correcting deficiencies to risk assessment of surfactants by Freeling et al. (2019), Science of The Total Environment, Volume 721, 2020, 135847, ISSN 0048-9697, https://doi.org/10.1016/j.scitotenv.2019.135847.

For Enzyme chapter

Sarlo K, Kirchner DB, Troyano E, Smith LA, Carr GJ, Rodriguez C. Assessing the risk of type 1 allergy to enzymes present in laundry and cleaning products: evidence from the clinical data. Toxicology. 2010 May 27;271(3):87-93. doi: 10.1016/j.tox.2010.03.007. Epub 2010 Mar 17. PMID: 20223268.

American Conference of Governmental Industrial Hygienists (ACGIH). (2011) TLVs and BEIs. Threshold limit values for chemical substances and physical agents & biological exposure indices. Cincinnati: ACGIH. ISBN: 978-1-607260-28-8.

Basketter D, Crozier J, Hubesch B, Manou I, Mehling A, Scheel J. Optimised testing strategies for skin sensitisation--the LLNA and beyond. Regul Toxicol Pharmacol. 2012 Oct;64(1):9-16. doi: 10.1016/j.yrtph.2012.06.003. Epub 2012 Jun 17. PMID: 22713689.

Basketter DA, Kruszewski FH, Mathieu S, et al. Managing the Risk of Occupational Allergy in the Enzyme Detergent Industry. J Occup Environ Hyg. 2015;12(7):431-437. doi:10.1080/15459624.2015.1011741

International Association for soaps, detergents and maintenance products (A.I.S.E.). Guidelines for the Safe Handling of Enzymes in Detergent Manufacturing. 2018 March. Version 2.2. https://www.aise.eu/documents/document/20180405111438-aise-enzymes_safe_handling-v2-2-march_2018.pdf

International Association for soaps, detergents and maintenance products (A.I.S.E.). 2021. Compositiob and Ingredients. https://cleanright.eu/en/composition-and-ingredients.html

International Association for soaps, detergents and maintenance products (A.I.S.E.). Activity & Sustainability Report 2020-21. https://www.aise.eu/documents/document/20210622092224-a_i_s_e__activity_sustainability_report_2020-21_web.pdf

Basketter DA, Broekhuizen C, Fieldsend M, Kirkwood S, Mascarenhas R, Maurer K, Pedersen C, Rodriguez C, Schiff HE. Defining occupational and consumer exposure limits for enzyme protein respiratory allergens under REACH. Toxicology. 2010 Feb 9;268(3):165-70. doi: 10.1016/j.tox.2009.12.014. Epub 2009 Dec 21. PMID: 20026217.

D. Basketter, N. Moreno, M. Simonsen
Occupational Exposure Limits for Enzymes: Practical Considerations; Int J Pul & Res Sci 5(1): IJOPRS.MS.ID.555651 (2021)

Cullinan P., J.M. Harris, A.J. Newman-Taylor et al.: An outbreak of asthma in a modern detergent factory. *Lancet 356*:1899–1900 (2000).

A.I.S.E., HCPA, AMFEP, ACI: The Role of Enzymes in Detergent Products. Factsheet (2021). https://www.aise.eu/cust/documentrequest.aspx?UID=ecaa311b-701c-4a50-83ea-f66963f04d87

HERA Project. 2005. α-AMYLASES, CELLULASES AND LIPASES (CAS No. 9000-90-2, 9012-54-8, 9001-62-1) Human and Environmental Risk Assessment on ingredients of Household Cleaning Products. Revised HERA Report, November 2005; https://www.heraproject.com/files/38-F-Hera_Bridging_document_28.10.05.pdf

For Preservatives chapter

International Association for soaps, detergents and maintenance products (A.I.S.E.). Preservatives: Key Biocidal Ingredients to Preserve Liquid Detergents (2018). https://www.aise.eu/cust/documentrequest.aspx?DocID=4375

Roell et. al., An Introduction to Terminology and Methodology of Chemical Synergy—Perspectives from Across Disciplines, Front. Pharmacol., April 2017 https://doi.org/10.3389/fphar.2017.00158

Anne S. Kienhuis, Wout Slob, Eric R. Gremmer, Jolanda P. Vermeulen, Janine Ezendam. A dose-response modeling approach shows that effects from mixture exposure to the skin sensitizers isoeugenol and cinnamal are in line with dose addition and not with synergism. Toxicological Sciences, 147:68–74, 2015. https://doi.org/10.1093/toxsci/kfv109

Anne Marie Api, David Basketter, James Bridges, Peter Cadby, Graham Ellis, Nicola Gilmour, Helmut Greim, Peter Griem, Petra Kern, Alain Khaiat, John O'Brien, Thomas Rustemeyer, Cindy Ryan, Bob Safford, Benjamin Smith, Matthias Vey, Ian R. White. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regulatory Toxicology and Pharmacology, 118:104805, 2020. https://doi.org/10.1016/j.yrtph.2020.104805

Ian R. Jowsey, David A. Basketter, Anita Irwin. Proliferative responses in the local lymph node assay associated with concomitant exposure to 1,4-phenylenediamine and methyldibromo glutaronitrile: evidence for synergy? Contact Dermatitis, 59:90–95, 2008. 10.1111/j.1600-0536.2008.01349.x

ECHA. Guidance on the Biocidal Products Regulation Volume III Human Health - Assessment & Evaluation (Parts B+C), December 2017 https://echa.europa.eu/documents/10162/23036412/biocides_guidance_human_health_ra_iii_part_bc_en.pdf/30d53d7d-9723-7db4-357a-ca68739f5094

For NaOH chapter

Aschberger K, Cosgrove O, De Coen W, Lund B, Pakalin S, Paya Perez A, Vegro S, editors. European Union Risk Assessment Report - Sodium Hydroxide. EUR 23040 EN. Luxembourg (Luxembourg): OPOCE; 2007. JRC41906 https://publications.jrc.ec.europa.eu/repository/handle/JRC41906

Sodium Hydroxide REAC Consortium. 2021. https://www.reachcentrum.eu/consortium/sodium-hydroxide-reach-consortium-161.html#

Euromonitor (2021). Market value of drain cleaners and over cleaners.

Alternatives to blanket MAF

Bauer, Franklin & Thomas, Paul & Fouchard, Samuel & Serge, Neunlist. (2018). High-accuracy prediction of Mechanisms of Action using structural alerts. Computational Toxicology. 7. https://doi.org/10.1016/j.comtox.2018.06.004

Bauer, Franklin & Todorov, Zlatomir & Thomas, Paul. (2021). An in silico battery to rule out chemicals with no endocrine disrupting potential on known targets. https://doi.org/10.13140/RG.2.2.17469.79841.

MechoApedia: https://www.kreatis.eu/MechoA/

McDonough K, Casteel K, Itrich N, Menzies J, Belanger S, Wehmeyer K, Federle T. 2016. Evaluation of anionic surfactant concentrations in US effluents and probabilistic determination of their combined ecological risk in mixing zones. Sci Total Environ 572:434–441.

Posthuma, L., Altenburger, R., Backhaus, T. et al. Improved component-based methods for mixture risk assessment are key to characterize complex chemical pollution in surface waters. Environ Sci Eur 31, 70 (2019). https://doi.org/10.1186/s12302-019-0246-5

Tralau, T., Oelgeschläger, M., Kugler, J. et al. A prospective whole-mixture approach to assess risk of the food and chemical exposome. Nat Food 2, 463–468 (2021). https://doi.org/10.1038/s43016-021-00316-7