EU CLP Regulation

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The EU Detergent Industry Network 'DetNet' – an industry approach for the EU CLP classification of detergent and cleaning products for skin and eye effects

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Abstract: The implementation of the EU CLP Regulation for mixtures in 2015 led to a reduction of the cut-off levels for mixtures containing severely irritating or corrosive ingredients. As a result, most everyday detergents would be required to carry the same corrosive pictogram on the label as caustic or highly acidic specialty cleaners. However, in most cases, calculation-derived skin and eye hazard classifications do not reflect in-market experience and consumer understanding of the hazardous properties of household detergents. The detergent industry responded to this situation by forming the Detergent Industry Network 'DetNet'. It is a transparent process that supports mixture classification decisions by sharing data, expertise, and best practices between manufacturers of detergent and cleaning products. At the core of DetNet is its database providing access to compositional information and toxicological data on more than 240 detergents and cleaning products. This paper describes and discusses the main features of DetNet, its organisational structure and database. Based on a case study, the process and functioning of DetNet to support a scientifically sound classification of an untested mixture for skin and eye effects based on data available for similar mixtures is demonstrated.

Keywords: EU CLP Regulation; skin and eye hazards; weight-of-evidence based mixture classifications; similar mixture concept

1 Introduction

The accurate classification and labelling of the hazardous properties of household products is a prerequisite for ensuring their safe handling and use by the consumer. Existing physico-chemical, environmental, and toxicological data as well as in-market information on the product formulations, are to be used in a scientifically sound, robust, and consistent manner to allow for classification decisions that reflect the products' inherent hazardous properties.

In Europe, the classification and labelling of chemical substances and mixtures is based on EU Regulation (EC) No 1272/2008.[1] The so-called European Union's Classification, Labelling and Packaging (EU CLP) Regulation sets the criteria to determine whether a substance or mixture displays physico-chemical, environmental, or human health properties that would warrant a hazard classification. Such classification is the starting point for hazard communication. For every hazard class and category, the CLP Regulation sets detailed criteria for the labelling elements such as pictograms, signal words and standard statements for hazard, prevention, response, storage, and disposal. It also sets general packaging standards to ensure the safe supply and use of hazardous substances and mixtures. The CLP Regulation is based on the United Nations' Globally Harmonised System (GHS).[1] It amended the Dangerous Substance Directive (67/548/EEC (DSD)),[2] the Dangerous

†This publication is dedicated to Gerard Luijkx, PhD, who had supported the A.I.S.E. for almost two decades and sadly passed away in 2023.

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Preparations Directive (1999/45/EC (DPD))[3] and the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EC) No. 1907/2006.[4] Since 1 June 2015, the CLP Regulation is the only legislation in force in the EU for classification and labelling of substances and mixtures. With its implementation, the EU became the first region globally to use the GHS mixture criteria for mixtures in general and consumer products specifically.

The CLP Regulation specifies in Articles 5 to 8 the type of information that should be considered in the hazard classification process. For assessing the human health hazards of mixtures, the hazard classification should preferably be based on toxicological information on the mixture itself. However, new testing may only be performed when all other means of generating information according to Article 8 of CLP have been exhausted. This includes the possibility of using alternative methods or approaches to animal testing such as use of existing data, *in vitro* or data on similar tested mixtures under consideration of the bridging principles in a weight of evidence manner. In the absence of such information, the CLP allows for the classification of mixtures on the basis of its ingredient classifications by application of the additivity method, taking into account the cut-off limits provided for each hazard class in the CLP Regulation.[1]

Historically, the use of the additivity method has been the preferred approach for determining product classifications by household cleaning and detergent product manufacturer with limited in-house expertise for assessment of the toxicological hazards associated with their products. However, the introduction of the CLP Regulation with its new lower cut-off levels for skin and eye hazard triggered more severe classifications if the additivity method is applied compared to the preceding DPD. For example, the cut-off level for triggering a 'Serious eye damage' (Eye Cat. 1) classification of a mixture is the presence of a single or multiple Eye Cat. 1 classified ingredients at concentrations equal or greater than 3 %. Under the DPD this threshold was ≥10 %. An Eye Cat. 1 classification goes along with the corrosive pictogram and the signal word 'Danger' on the product label. As a result, most daily-use detergents would be classified as Eye Cat. 1 and therefore carry the same corrosive pictogram on the label as caustic or highly acidic specialty cleaner suggesting to the consumer that both product types have the same hazards. It has been estimated that because of the move from DPD to the CLP Regulation and using the additivity method that the percentage of the total household product portfolio being labelled as corrosive will increase from 6 to 55 %.[1] This is largely related to the fact that household detergent and cleaning products contain surfactants at concentrations greater than 3 %. In neat form, surfactants are typically classified as Eye Cat. 1. The differences between DPD and CLP in cut-off levels for 'Serious eye damage' (Category 1) classified ingredients are illustrated in Figure 1.

It is without saying that product hazards need to be correctly identified to ensure safe and sustainable product use. Even though the additivity method is a recommended CLP method to determine the classification of mixtures, in-market data from a recent multicentre prospective poison control centre ('MAGAM II') study[5] strongly suggests that the application of the current threshold for skin or eye irritation or corrosion leads to an over-classification particularly of surfactant-based products. The MAGAM II study prospectively investigated the effects of human eye exposures to household cleaning products including dishwashing liquids and laundry detergents. Over a period of 24 months, the study did not reveal any severe eye effects after accidental exposure to household detergent or cleaning products. Follow-up by ophthalmologists demonstrated that reported irritation effects were fully reversible within a few days after exposure.[5]

The CLP permits a way out of this dilemma by allowing the use of existing data on similar tested mixtures or the generation of new *in vitro* data. Any methods used must be adequate, relevant and reliable for the type of mixture and hazardous effect to be evaluated. The classification of detergent and cleaning products for skin and eye effects based on existing or new data requires substantial experience of the effects of surfactant-based products *in vitro* or *in vivo* test systems. For example, surfactant-based products often display eye irritation profiles that would trigger an eye irritant ('Eye Cat. 2'), but not a severe eye hazard classification ('Eye Cat. 1'). Unfortunately, no *in vitro* method has been validated yet that allows the identification of Eye Cat. 2 irritants. Hence, in the absence of an Organization for Economic Cooperation and Development test guideline (OECD TG) 405 compliant *in vivo* study, an Eye Cat. 2 classification can only be justified by using information from a range of sources in a weight of evidence manner.[6]

In response to the challenges posed by the CLP Regulation to the detergent industry, the International Association for Soaps, Detergents and Maintenance Products ('A.I.S.E.') formed the Detergent Industry Network 'DetNet'. DetNet is a voluntary initiative that supports manufacturers of detergent and cleaning products in establishing correct eye and skin hazard classifications of their detergent mixtures. It is anchored in Annex I of the CLP Regulation which requests the cooperation of suppliers within an industry sector to foster the sharing of data, expertise and best

1 A.I.S.E Factsheet: Classification and labelling of detergents under CLP. December 2017.

EU Dangerous Preparation Directive (1999/45/EC) versus EU CLP Regulation (EC) No. 1272/2008 Mixture classification threshold for Eye Cat. 1 ingredients		
DPD Classification threshold; Indication of danger Risk phrase: Pictograms	Concentration [%]	CLP Classification threshold, Signal word, Category Hazard statement, Pictograms
≥ 10 %  Irritant "Risk of serious damage to eyes"	10-100	 ≥ 3 % DANGER Eye Cat.1 "Causes serious eye damage"
≥ 5 to 10 %  Irritant "Irritating to eyes"	5-10	
0 to 5 %: no labelling	3-5	
	1-3	 ≥ 1 to < 3 % WARNING, Eye Cat. 2 "Causes serious eye irritation"
	0-1	0 to < 1 %: no labelling

Figure 1: DPD versus CLP additivity rules for 'Serious eye damage' (Eye Cat. 1) ingredients.

practices in the context of classification and labelling of their products through formation of a network.[1]

DetNet is a secure web-based information technology (IT) system containing a database with skin and eye irritation testing data for more than 240 detergent and cleaning products. However, DetNet is more than just a database. It is a transparent process that supports high quality classification decisions by sharing toxicological data and expertise residing within the detergent industry and by providing regular training and guidance of its users on all elements critical to the classification of new, untested mixtures based on existing data for skin and eye effects. This includes for example the correct interpretation of *in vitro* and *in vivo* skin or eye irritation data, application of the weight of the evidence and mixture similarity assessments using expert judgement. Only nominated company experts that have the appropriate scientific credentials and meet the eligibility criteria established by an external Scientific Advisory Panel are entitled to use DetNet. To ensure highest possible degree of transparency, national classification and labelling (C&L) enforcement authorities receive access to the DetNet tool upon request.

The objective of this paper is to describe the main features of DetNet, its organisational structure and database contents of DetNet as a tool to support the scientifically sound classification of a new, untested detergent mixture for skin and eye irritation/corrosion based on test data available for similar mixtures identified via DetNet is demonstrated and discussed.

2 Experimental procedure

2.1 The DetNet tool

The overall aim of DetNet is to provide manufacturers and suppliers of detergents and cleaning products with data and expertise for the assessment of the skin and eye effects of newly developed product formulations based on existing information on similar mixtures. The following provides an overview of the organizational structure of DetNet, its database and the processes that are in place to ensure the safety and regulatory compliance of detergent mixtures for skin and eye effects while simplifying, harmonizing, and accelerating the classification process.

2.2 Organizational structure and process

At the core of DetNet is its database providing access to compositional and toxicology data on more than 240 detergent and cleaning products. As stated before, DetNet is more than

just a database. It is a transparent process that supports high quality classification decisions by sharing toxicological data and expertise residing within the detergent industry and by providing regular training and guidance of its users on all elements critical to the classification of new, untested mixtures for the skin and eye effects based on existing data.

The DetNet tool can only be used by accredited scientists. Prior to being able to access the DetNet database, member company nominees are required to meet established eligibility criteria about their scientific qualifications and regulatory knowledge, expertise in the field and to stay abreast of any updated toxicological and regulatory guidance provided by the A.I.S.E. technical task forces. DetNet users may not only be company internal scientists. DetNet member companies without the required in-house experience and expertise can also nominate external experts, scientists from academia or specialised consultants that meet the required DetNet eligibility criteria.

Via a secure web-based tool, the eligible user can identify in the DetNet database mixtures with skin and/or eye data that are similar to an untested mixture for which the user wishes to determine skin and/or eye hazard classifications. In case the user concludes that the identified mixture and its data are suitable for the classification of his untested mixture, he can move forward with preparing the classification record (CR) by completing the CR mask provided by the tool. The CR mask requires a detailed side by side comparison of the tested and untested mixture in terms of product category, pH and reserve alkalinity/acidity and composition for a final confirmation of mixture similarity. Once confirmed, the user completes the classification record by confirming the new mixtures skin and/or eye classification, the method used to derive the classification and a detailed justification of the classification decision. The user can revisit a detailed mixture comparison screen at any time during the CR completion process. The final classification record can be downloaded from the system and should be kept on file by the company to support a classification decision of a marketed product via DetNet in case of an inspection by a national CLP enforcement authority. If the enforcement authorities require more detailed information, the DetNet process foresees detailed procedures in terms of data sharing to provide the authorities with the means to reproduce the basis of a companies' product classification decision.

It is of important note that DetNet neither proposes a classification for an untested mixture nor does it constitute any kind of recommendation or expert assessment. It only presents potentially relevant information without any ranking which may be used by a user to support the classification of an untested mixture. The responsibility for the correct classification, labelling and packaging of mixtures in accordance with the EU CLP Regulation rests with the DetNet member company that places the product on the market.

The overall process is administrated by the DetNet management which resides within the A.I.S.E. The dedicated DetNet manager ensures together with the IT tool developer the effective and secure functioning of the web-based tool, confirms with the data owners the acceptability of the formulation and testing information prior to entering into the database, reviews the qualifications of nominated company experts against eligibility criteria and coordinates with the technical industry task forces the development/updating of required technical guidance documents and organizes regular user trainings. Specifically, the latter two functions are critical to assuring the quality of any classification decisions being made by member companies via use of information derived from the DetNet tool. The A.I.S.E. technical task forces are guided and supervised by an external scientific advisory panel (SAP) which is comprised of industry-independent experts from academia or poison control centers in the field of toxicology, dermatology or ophthalmology. Figure 2 illustrates the organisational structure of DetNet.

2.3 DetNet tested mixture database

The DetNet database contains detailed compositional information and data on detergent and cleaning products that have been previously tested for skin and eye irritation/corrosion. To assure confidentiality and trade secrets, the names of companies providing the tested mixtures and data as well as trade names are not disclosed. The DetNet secretariat maintains a system of naming and coding of formulation and data to assure trade secrets and confidentiality.

Compositional information and data critical for the classification of mixtures for skin and eye irritation/corrosion are submitted by the data owner to the DetNet secretariat along with the respective robust study summary in a standardised tested mixture sharing format. Information on the product category, physico-chemical properties (i.e., physical form, pH of liquid mixture or 10 % solution for powders and reserve alkalinity/acidity if pH is ≤2 or ≥11.5) and ingredients are to be submitted. All ingredients that are classified as skin or eye irritant/corrosives and are present in the tested mixture at concentrations ≥1 % are required to be identified by chemical name, chemical class, chemical abstracts service (CAS) number and concentration in mixture (as % w/w). Ingredients not classified for skin or eye irritation/corrosion and present at concentrations ≥1 % which may impact the irritation/corrosion profile of the mixture (e.g., skin penetration enhancer such as alcohols, solvents, or

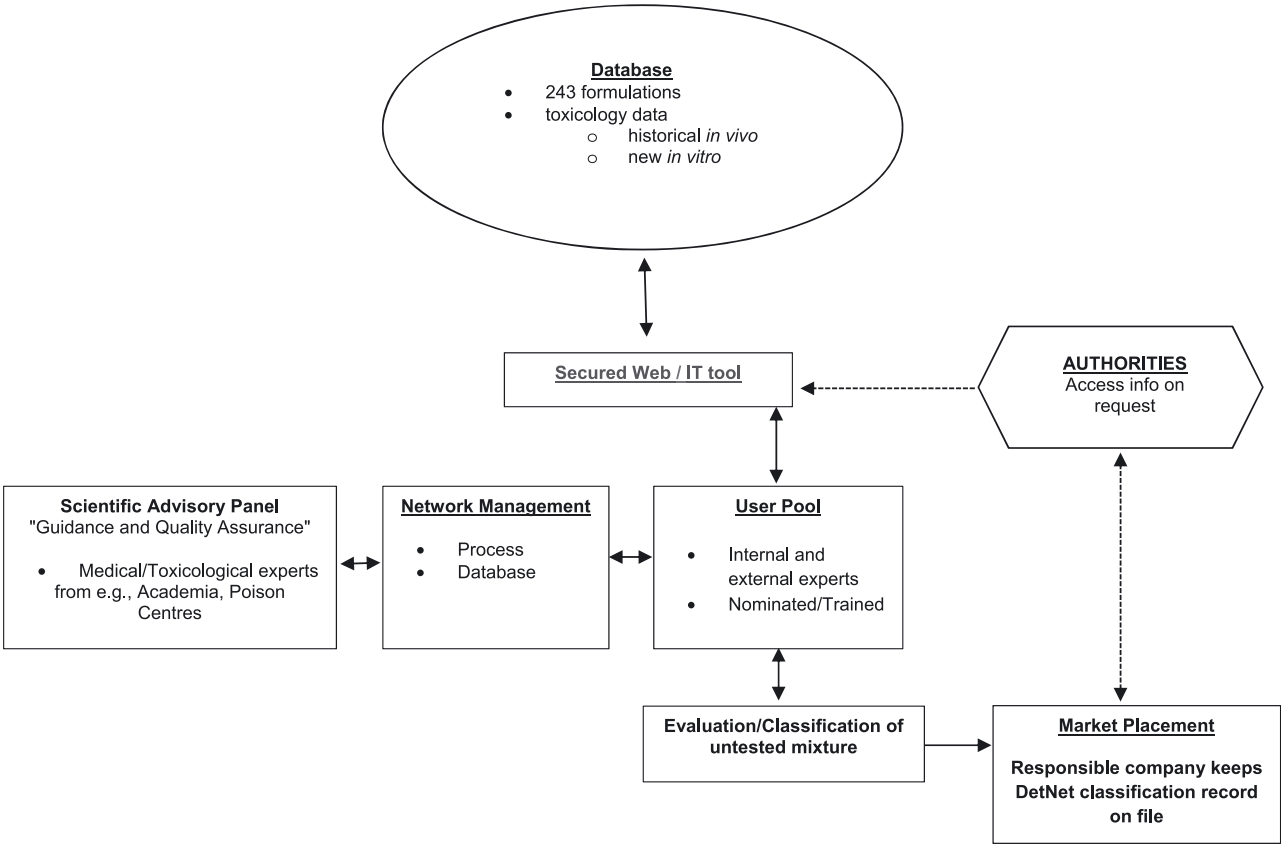

Figure 2: Organisational structure of DetNet.

soaps) should also be declared by name, CAS numbers and concentrations. Any other ingredients present in the test mixture not classified for skin or eye effects and not considered to contribute to the skin or eye irritation profile of the mixture should at the minimum be declared generically by ingredient type (e.g., chelator, bleach activator, builder, fragrance, preservative). Declaration of ingredients as per the data sharing format may mean that the composition does not add up to 100 %.

Table 1 provides an overview of the number and type of tested mixtures contained in the DetNet database. Currently, DetNet includes a total of 243 test mixtures covering laundry liquids and powders, hand dishwashing liquids, all-purpose cleaner, acidic liquid cleaner and alkaline bleaches. These mixtures have been tested in a total of 342 studies for skin and eye irritation out of which 121 studies have been conducted *in vitro*, 144 studies in experimental animals and 92 studies in humans (i.e., confirmatory human patch testing for skin compatibility according to the Draize skin irritation grading scale). A more detailed break-down of the studies contained in DetNet is provided in Table 2. All studies have been quality-rated according to the Klimisch criteria[7] and summarized in a robust study summary (RSS) format based on the original study report.

Table 1: Break-down of tested mixtures contained in DetNet according to product categories.

Product category	Number of tested mixtures
Powder laundry detergent	103
Liquid laundry detergent	50
Hand dish wash detergent	40
All-purpose cleaner	30
Acid liquid cleaner	10
Alkaline liquids/bleach	10

Table 2: Number of skin and eye irritation studies contained in DetNet.

Study protocol	Total
Skin irritation	
OECD TG 439 (*in vitro*)	39
OECD TG 404 (*in vivo*)	8
4 h human patch test (OECD TG 404 based skin grading scale)	92
Eye irritation	
OECD TG 438 with histopathology (*in vitro*)	67
Modified OECD TG 405 (*in vivo*; 'LVET')	127
OECD TG 405 (*in vivo*)	9

2.4 Quality assurance

To assure the quality of the DetNet classification process and thereby increase the confidence into the outputs provided by the DetNet tool, the following elements have been incorporated into the process:

- Stringent eligibility criteria for DetNet users;
- Only mixture composition and study data meeting stringent quality criteria are entered into the DetNet database;
- Regular guidance and training of DetNet users by industry experts to instruct on any scientific developments and regulatory changes of relevance to the skin and eye effects assessment of detergent mixtures;
- Supervision of the technical quality of the DetNet process by an external scientific advisory panel (SAP).

It is of utmost importance that only qualified representatives from member companies are eligible to use DetNet. While the CLP Regulation does not specify the qualification profile of a scientist taking hazard classification decisions, A.I.S.E. technical expert groups established in collaboration with an external SAP has established such criteria for users prior to being accredited to use DetNet. In addition to demonstrating their scientific credentials evidenced by a BA, MSc or PhD in toxicology, chemistry, pharmacology or related life science, a DetNet applicant is expected to demonstrate broad professional experience and knowledge in the toxicological profile of detergent mixtures; the function and toxicological profile of ingredients contained in detergent and cleaning products; chemical and physico-chemical factors that can impact the skin and eye irritation/corrosion profile of a detergent mixture and hence classification and labelling requirements; test systems including protocols and scoring schemes available for the assessment of the skin and eye hazards of substances and mixtures; and the regulatory provisions by the CLP for C&L of substances or mixtures for hazardous properties. Eligible users should also have experience in discussing similar mixture-based classifications with regulatory authorities.

Another important element in assuring scientifically sound and CLP conform classification decisions via use of the DetNet tool is the ongoing access of the users to the toxicology expertise and experience that resides within the detergent industry. This is made available through a series of technical guidance documents addressing the key aspects to be considered when classifying untested mixtures on the basis of similar mixture data identified in the DetNet database. This ranges for example from the identification of chemical factors impacting a mixture's skin and eye irritation/corrosion profile (e.g., potential drivers for synergist or antagonistic effects; pH and reserve alkalinity/acidity) to the discussion of the suitability of available non-testing and testing methods for the assessment of the skin and eye irritation/corrosion profile of detergent mixtures. Moreover, considering the CLP requirement to consider all available information bearing to the determination of a hazard in a Weight of Evidence (WoE) manner, substantial guidance and training is provided to the user in how to build and transparently document a WoE-based classification decision for skin and eye irritation/corrosion. Existing guidance documents and trainings are regularly updated to adjust for any scientific and regulatory changes for the endpoints of interest.

A final component in assuring the quality of DetNet-based classification decision is the installation of an SAP within the process. The SAP which is composed of industry-independent experts from academia or poison control centres in the field of toxicology, dermatology or ophthalmology advises and provides input on the DetNet user eligibility criteria and reviews and endorses the technical guidance documents developed and updated by A.I.S.E.'s technical task forces. The SAP's role is also to supervise the DetNet process and to identify any technical issues including data gaps and method validation requirements as well as additional training needs of the DetNet users.

3 Results

3.1 Determination of a detergent product classification for skin and eye effects using the DetNet tool

The scheme presented in Figure 3 presents the approach being practically applied to support the classification of a new, untested detergent mixture for skin and eye irritation/corrosion via the use of the DetNet tool.

In line with the CLP Regulation, the process starts with the collection of all available information pertinent to the skin/eye hazard assessment followed by a verification if, relative to a previously tested mixture, the permitted variation, dilution or batching bridging principles can be applied. If this is not the case, the DetNet database will be searched for similar mixtures that have been tested for skin and/or eye irritation. In case one or multiple tested mixtures with data suitable for classification purposes can be identified, the assessor verifies the feasibility of applying the bridging principles 'interpolation within one toxicity category' or 'substantially similar mixture'. In case these principles are applicable, the untested detergent mixture can be classified according to the identified tested mixture(s).

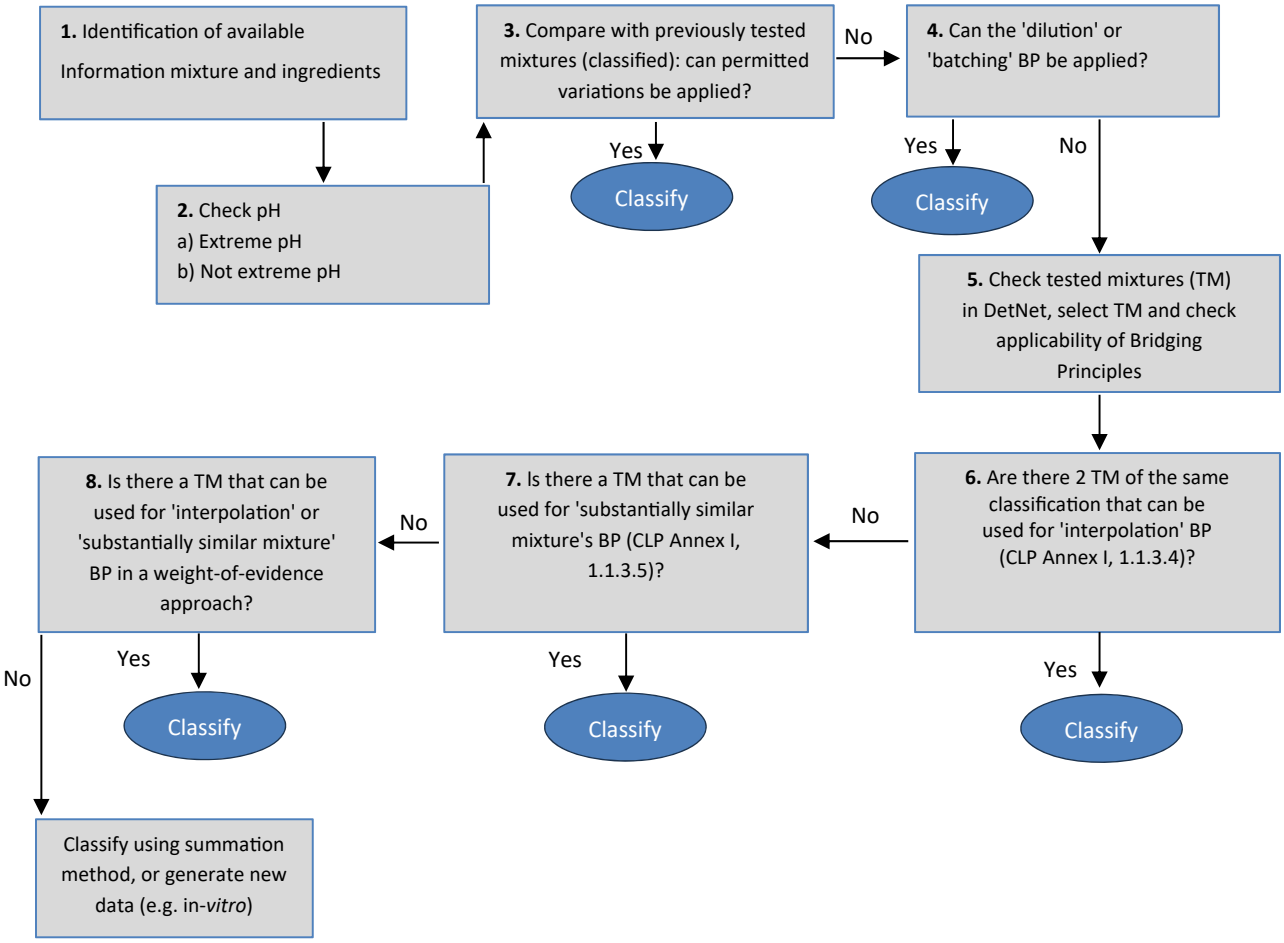

Figure 3: Practical approach for classifying new mixtures for skin and eye effects.

The principles 'interpolation within one toxicity category' and 'substantially similar mixture' are the most relevant bridging principles for comparison of a tested mixture with a new mixture in the detergent and cleaning product range. While rules for the application of these principles are provided in the CLP Regulation and guidance is provided, there is room for different interpretations, especially on the aspect of ingredient sameness. This is largely because surfactants, a major component of detergent products, are complex, most often unknown or variable composition, complex reaction products or biological materials' (UVCB)-type substances for which substance naming rules have changed under the REACH Regulation.[4] In such cases where ingredient sameness, but not the hazard category is impacted, CLP offers the possibility to classify the untested mixtures on the basis of similar mixture data using a weight of evidence approach, even though the CLP criterion 'substantially similar mixture' may not have been met in its strictest sense.

If the assessor comes to the conclusion that a similar mixture is not 'similar enough' leading to an uncertainty in the hazard assessment of the new mixture, the DetNet process recommends the generation of additional *in vitro* data for hazard classification purposes or, if resource-wise not feasible, the application of the additivity method for the determination of the classification of the mixture under consideration of the cut-off levels provided in the CLP Regulation. In case of additional testing, it should be noted that there is currently no officially validated *in vitro* method allowing to support an eye Cat. 2 classification of a substance or mixture. In the absence of OECD TG 405 conform *in vivo* data, such classification can only be supported via a WoE-based approach.

3.2 Case study

The DetNet-based classification process can be best illustrated by a real-life example. For this purpose, a hand dishwashing liquid, codified as 'HDWL1', with a formulation similar to those currently on the market has been chosen.

HDWL1 is viscous liquid with a product pH of 7 containing a total of 47 % anionic surfactants, an alkylbenzene sulfonate ('LAS-Na') at 32 % and a fatty alcohol ethoxysulphate ('AES') at a concentration of 15 %. Under CLP, both surfactants are classified as damaging to eyes (i.e., Eye Damage Cat. 1) and irritating to skin (i.e., Skin Irritation Cat. 2). HDWL1 contains further a solvent system composed of propane-1,2 diol at 9 % and ethanol at 3 %. Propane-1,2 diol is neither classified for skin nor for eye hazard. Ethanol is classified as irritating to eyes (i.e., Eye Irritation Cat. 2). The detailed composition of HDWL1 and its ingredient classifications are provided in Table 3.

The process of identifying a similar tested mixture in the DetNet database is started by entering the untested mixture details into the Tested Mixture Search input form in DetNet.

Table 3: Composition of untested mixture HDWL1.

Product category			Hand dishwashing liquid
Code/mixture number			HDLW1
Physical form			Viscous liquid
pH			7.0
Acid/alkaline reserve			0.0
Ingredient	**% (w/w) in mixture**	**CAS #**	**CLP classification for skin and eye effects**
Anionic surfactant			
Benzenesulfonic acid, C_{10-13}-alkyl derivs., sodium salts	32	68411-30-3	Skin irritation Cat. 2 serious eye damage Cat. 1
Alcohols, C_{12-14} (even numbered), ethoxylated <2.5 EO, sulfates, sodium salts	15	68891-38-3	Skin irritation Cat. 2 serious eye damage Cat. 1
Solvent			
Ethanol	3	64-17-5	Not classified as hazardous to skin eye irritation Cat. 2
Propane-1,2-diol	9	57-55-6	Not classified as hazardous to skin or eyes
Organic acid			
Carboxylic acids, di-, C_{4-6}	1	68603-87-2	Not classified as hazardous to skin serious eye damage Cat. 1
Perfume			
Perfume mix 1	0.7	N/A	Not classified as hazardous to skin or eyes
Minor			
Water	39.3	7732-18-5	Not classified as hazardous to skin or eyes
Total	100 %		

This includes initially the product category, physical form, pH and, if applicable, reserve alkalinity/acidity according to Young et al.[8] The ingredients in the untested mixture are then entered with their chemical names, CAS numbers and their % w/w level in the mixture. For transparency and reproducibility reasons, the full composition (i.e., 100 %) of the untested mixture has to be entered. The system does not allow searching for tested mixtures if the entered ingredients of the untested mixture do not add up to 100 %.

A series of search filters are available in the tested mixture search input form. These search filters allow tailoring and limiting the output of the tool in terms of identified test mixtures to the specific product type and the type and concentrations of ingredients present in the untested mixture. These range from product category, pH and physical form to ingredient-specific search filters such as percentage of surfactants, total percent of skin/eye Cat 1 or 2 ingredients or total percent of penetration enhancing solvents or alcohols. The search results are impacted by the number of search filters selected in parallel. It is generally advisable to search the database with filter combinations focusing on those parameters within the untested mixture that are considered to be most critical to the skin or eye irritation endpoint. For the skin or irritation/corrosion assessment of untested mixture HDWL1, these are 'total % skin Cat. 2 ingredients' or 'total % eye Cat. 1 ingredients', 'total % surfactants' and 'total % solvents'. Of the 22 HDWL mixtures for which skin and the 32 HDWL formulations for which eye effects data are available, only 2 of the identified tested mixtures matched on all 3 search filter. In the database, these mixtures are codified as 'C4' and 'C8'. Table 4 presents the composition of untested mixture HDWL1 in comparison to the identified tested mixtures 'C4' and 'C8'.

As can be seen in Table 4, the tested mixture 'C8' matches the untested mixture HDWL1 better in terms of surfactant families and total % eye Cat. 1 and skin Cat. 2 classified surfactants (i.e., 50 % versus 47 %) compared to tested mixture 'C4'. Mixture C4 is composed of a mixture of anionic, non-ionic and amphoteric surfactants from different surfactant families and contains 8–10 % less eye Cat. 1 and skin Cat. 2 classified surfactants compared to the untested mixture HDWL1 and C8 respectively. Penetration enhancing solvents are contained in all three mixtures at comparable levels. Likewise, product pH and viscosity are in a similar range.

Based on chemical factors known to drive skin and eye irritation potential of a hand dishwashing liquid, tested mixture C8 is assessed to be most similar to the untested mixture HDWL1. Hence, the skin and eye data available for mixture C8 is considered to be adequate and relevant for the assessment of skin and eye hazards of HDWL1. Neither the

Table 4: Composition of untested mixture HDWL1 in comparison to tested mixtures 'C4' and 'C8'.

Ingredient	CAS#	Skin classification	Eye classification	Untested mixture 'HDWL-1'	Identified text mixture 'C8'	Identified text mixture 'C4'
Anionic surfactant				47 %	50 %	32 %
Sulfuric acid, mono-C_{12-14}-alkyl esters, sodium salts	85586-07-8	Skin irritation Cat. 2	Serious eye damage Cat. 1			12 %
Alkyl (C_{12-14}) ether sulphate 3–4 EO, sodium sail	68891-38-3	Skin irritation Cat. 2	Serious eye damage Cat. 1			10 %
Benzenesulfonic acid, C_{10-13}- alkyl derivs., sodium salts	68411-30-3	Skin irritation Cat. 2	Serious eye damage Cat. 1	32 %		
Alcohols, C_{12-14} (even numbered), ethoxylated <2.5 EO, sulfates, sodium salts	68891-38-3	Skin irritation Cat. 2	Serious eye damage Cat. 1	15 %	15 %	10 %
Benzenesulfonic acid, mono C_{9-14}-alkyl derivs., compds. with triethanolamine		Skin irritation Cat. 2	Serious eye damage Cat. 1		35 %	
Non ionic surfactant				–	–	45 %
D-GIucopyranose, oligomeric, C_{10-16} (even numbered) alkyl glycosides	110615-47-9	Skin irritation Cat. 2	Serious eye damage Cat. 1			45 %
Amphoteric surfactant				–	–	35 %
1-Propanaminium, 3-amino- N-(carboxymethyl)-N,N-dimethyl-,N-coco acylderivs., hydroxides, inner salts	61789-40-0	Skin irritation Cat. 2	Serious eye damage Cat. 1			35 %
Solvent				12 %	10 %	10 %
Ethanol	64-17-5	Not classified as hazardous to skin	Eye irritation Cat. 2	3 %	3 %	10 %
Propane-1,2-diol	57-55-6	Not classified as hazardous to skin	Not classified as hazardous to eyes	9 %	7 %	
Organic acid				1 %	2.40 %	3.70 %
Carboxylic acids, di-, C_{4-6}	68603-87-2	Not classified as hazardous to skin	Serious eye damage Cat. 1	1 %	2.40 %	3.70 %
Perfume				0.70 %	N/A	0.70 %
Perfume mix	N/A	Not classified as hazardous to skin	Not classified as hazardous to eyes	0.70 %	Confidential	0.70 %
Minors				39.8 %	Balance	Balance
Water	7732-18-5	Not classified as hazardous to skin	Not classified as hazardous to eyes	39.8 %	Balance	Balance
Total				100 %	100 %	100 %

differences in carbon chain length distribution (i.e., C_{10-13} versus C_{9-14}) nor the different counter-ion in the benzenesulfonate (I.e., 'LAS-Na' vs. 'LAS-TEA') are assessed to impact the irritation/corrosion profile of HDWL1 versus C8. Both benzenesulfonates are in the same hazard skin and eye hazard class. The slightly higher surfactant level in C8 compared to HDWL1 adds additional conservatism to the assessment. All other minors contained in the mixtures are not relevant to the endpoint of skin or eye irritation/corrosion.

Mixture 'C8' has been tested for eye and skin irritation/corrosion *in vitro* as well as *in vivo*. For skin effects, it was tested *in vitro* in a GLP compliant EpiSkin™ skin irritation test according to OECD TG 439[9] and *in vivo* in a GCP compliant 4-h human patch test.[10] The quality of both studies was rated with a Klimisch score of 2. The EpiSkin™ skin irritation test which included also positive and negative controls revealed a relative individual tissue viability of 63.6 % (±6.7 % SD) leading the conclusion that C8 does not require a skin irritant classification under the EU CLP Regulation.[1] This *in vitro* result is confirmed by the results obtained in the 4 h human patch test. In this study, the semi-occlusive application of C8 on the upper arms of 10 volunteers for 4 h resulted in a mean erythema score of 0.1 and a mean oedema score of 0 at the readings after 24, 48 and 72 h after patch removal.

The eye effects of C8 were evaluated in an Isolated Chicken Eye Test (ICE) according to OECD TG 438 with the addition of histopathology OECD[11] and in an *in vivo* rabbit eye irritation study according to a modified OECD TG 405

testing protocol (LVET).[12] The quality of the ICE study was rated with a Klimisch score of 1 and that of the LVET with a Klimisch score of 2. The latter indicates that the LVET study is well documented and scientifically acceptable, but not in full compliance with the OECD TG 405 testing protocol. The ICE revealed an Irritation Index of 84 suggesting a moderate eye irritation potential of mixture C8. Applying the ICE standard test method criteria only, does not allow the exact determination of a CLP eye hazard category (i.e., 'No Prediction Can be Made'). Taking into account the histopathological information generated in the study as advocated by A.I.S.E. and recently considered in the update of OECD TG 438,[13] mixture C8 warrants a classification of EU CLP Category 1 for eye effects ('Serious Eye Damage') due to its moderate or severe erosion of the epithelium which was observed in 2 out of 3 corneas. No abnormalities of the stroma and endothelium were, however, observed. The LVET revealed some minor effects on the cornea and iris (i.e., mean score <1 observed in 1 out of 3 animals; 2 animals without effects), but stronger effects on the conjunctiva in terms of redness and chemosis (i.e., mean scores of 2.6 for redness and 1.2 for chemosis across 3 animals at 24, 48, and 72 h reading points). All effects were cleared within the 21 days observation period. The conjunctival effects observed in the LVET would trigger a Category 2 'eye irritation' classification for eye effects of C8 under the CLP Regulation.

3.3 Case study discussion and conclusions

The use of the DetNet tool allowed the identification of two tested mixtures of similar composition to the untested mixture HDWL1. Both mixtures were tested in good quality *in vitro* and *in vivo* skin and eye irritation/corrosion studies. All studies were assessed to be suitable for CLP classification purposes either on their own right or in combination on a weight of evidence basis. The closer examination of both mixtures in terms of composition and chemical drivers for skin and eye irritation known for dishwashing liquids allowed some prioritisation of one versus the other. Tested mixture C8 was judged to predict the skin and eye irritation potential of untested mixture HDWL1 better than tested mixture C4 while adding an additional degree of conservatism to the overall assessment.

Decisions on the classification and labelling of mixtures under the EU CLP Regulation should take into account all available relevant and adequate information pertaining to the effect in question on a weight of evidence basis. Following this principle, the untested mixture HDWL1 does not warrant a classification for skin irritation/corrosion under the EU CLP Regulation. This classification is primarily supported by the results obtained for the similar mixture C8 in a GLP compliant EpiSkin™ skin irritation test according to OECD TG 439[9] and a GCP compliant 4 h patch test in humans.[10] Both studies identified only a minor potential of C8 to cause skin irritation, below the criteria triggering a Category 2 skin irritant classification under the EU CLP Regulation. Moreover, neither physico-chemical nor data from other similar mixtures identified in the process (e.g., C4) or human experiences with similar mixtures on the market suggest the need for an irritant classification of HDWL1.

The situation is more heterogeneous for the eye hazard assessment of HDWL1 from a C&L point of view. The information provided by standard *in vitro* and *in vivo* toxicology studies with C8 (i.e., OECD TG 438 without consideration of histopathology, rabbit Low Volume Eye Test) as well as data from other similar mixtures identified in the process (e.g., C4) or human experiences with similar mixtures on the market suggest only a moderate irritation potential warranting at maximum an eye Category 2 classification under CLP.[6] However, the additional consideration of the histopathology included into the ICE with C8, but also C4 (information not presented)[13] point to more severe effects at the eye epithelium level under the conditions of the ICE *in vitro* assay which, according to the criteria developed by A.I.S.E. and considered in most recent update of the OECD TG 438,[11] point to the need of classifying HDWL1 for severe eye effects. Hence, to assure conservatism in the hazard assessment, the untested mixture HDWL1 is proposed to be classified as EU CLP Category 1 ('Serious Eye Damage') for eye effects.

4 Discussion

The introduction of the EU CLP Regulation in 2008 and its final implementation for mixtures in 2015 caused a number of challenges to the detergent industry. A major issue was the lowering of the cut-off levels for mixtures containing Skin Cat. 1 and Eye Cat. 1 ingredients. Relative to the former EU Dangerous Preparation Directive this change would result in severe hazard classifications going along with corrosive pictogrammes on the product label for the majority of the daily-use detergents in the household if, as often done by manufacturer with limited in-house toxicology resources, the additivity rules are being applied to determine mixture classifications (see Figure 1).

In most cases, calculation-derived hazard classifications ('additivity method') do not reflect actual industry experience of the actual hazardous properties of household detergents. This poses the risk of confusing the consumer

and a devaluation of the on-pack warning labels. The consumer may not be able to distinguish the hazards of truly corrosive products such as drain or specialty cleaners from non-corrosive daily-use detergents such as fabric conditioner, dishwashing or laundry liquids, a concern that has also been raised by national poison control centres. In-market data from a recent multicentre prospective poison control centre study ('MAGAM II') investigating the effects of accidental human eye exposures to household cleaning products including surfactant-containing dishwashing liquids and laundry detergents over a period of 24 months did not reveal any irreversible ('corrosive') effects.[5]

Under the umbrella of the A.I.S.E., the detergent industry responded to this challenge by forming the Detergent Industry Network 'DetNet'. Anchored in Annex I of the CLP Regulation, DetNet is a voluntary initiative that fosters the sharing of data, expertise and best practices amongst the manufacturers of detergent and cleaning products to support scientifically accurate and regulatory compliant product classifications in the industry sector. DetNet's organisational structure, database, process and steps implemented to assure reproducible, high quality classification decisions by DetNet users have been described in detail in Chapters two and three of this article.

Since inception of the DetNet process and the launch of the tool in 2013, DetNet member companies have officially completed classification records (CR) for more than 1,770 detergent and cleaning products. Considering different product variants on the market (e.g., perfume flankers) which do not require additional assessment as they fall under the permitted variation principle, one can conservatively estimate that more than 3,400 household products marketed in the EU have been classified via information derived from the DetNet tool. None of these products were tested *in vivo* for classification purposes, although there is currently no *in vitro* method available that has been validated to identify mixtures (or substances) requiring an Eye Cat. 2 classification for eye irritation.

An often-overlooked beneficial aspect of DetNet has been its impact on the understanding and in some cases enhancement of the performance of *in vitro* skin or eye irritation/corrosion testing methods for detergent-type products. The concept and idea behind DetNet triggered substantial funding of additional *in vitro* method evaluation and refinement work. Although most *in vitro* protocols in use for the assessment of skin or eye irritation/potential of substances and mixtures were also validated by the OECD for classification purposes, there was only little consideration of how these methods perform for detergent and cleaning products. Hence, established applicability domains of the assays were of little relevance for the detergent industry. To overcome this, specific *in vitro* testing programmes were put in place by the detergent industry to investigate the applicability of OECD validated *in vitro* skin or eye irritation/corrosion protocols for non-extreme pH but also extreme pH detergent and cleaning product mixtures. Of specific note is the detergent industry's engagement in determining the applicability domains of OECD testing guideline 438, the ICE, for assessing the ocular effects of detergent and cleaning product mixtures. In this context, the DetNet database provided access to a large set of relevant detergent mixtures for which a substantial amount of *in vivo* information could be made available. The benefit was not only to establish the overall list of possible mixtures to be evaluated but also to facilitate understanding of their relevance to being included in the *in vitro* testing programme.

The analysis of the *in vivo* data allowed the identification of the detergent mixture's drivers for eye corrosion classification, specifically regarding severity and persistence of effects. It thereby led to a better understanding of the *in vitro* methods performance for detergent mixtures as it focussed on improving the prediction of eye Category 1 mixtures based on persistence and severity of effects *in vitro*. For this purpose, a total of 23 non-extreme pH mixtures representing the four A.I.S.E. product categories 'laundry granules', 'laundry liquids', 'dishwashing liquids' and 'all-purpose cleaners' which were identified in DetNet were included into the *in vitro* eye irritation/corrosion testing programme. This part of the *in vitro* programme, which led to the addition of histopathology criteria to the ICE test protocol has been published in the peer reviewed literature.[13] Furthermore, 18 extreme pH products (i.e., acid and alkaline) which are not yet in the DetNet but for which *in vivo* information was made available by DetNet member companies were also evaluated in the ICE.[14]

Most recently, the incorporation of histology as an additional endpoint to better predict eye Category 1 non-extreme pH detergent and cleaning products has recently obtained regulatory acceptance through revision of OECD Test Guideline 438.[11] In this context, A.I.S.E.'s *in vitro* team was instrumental in conducting the predictive capacity and the inter-laboratory reproducibility programmes which demonstrated the acceptability of incorporating histology as and additional endpoint into the OECD TG 438. Although the testing programme with the extreme pH products is so far of little relevance yet as only few extreme pH products are contained in DetNet, the inclusion of these products into the *in vitro* programme contributed to establishing of the applicability domain of OECD TG 438.

Undoubtedly, a key strength of the DetNet process is the data and expertise sharing within the detergent industry sector leading to a simplified, reliable and harmonized way

of classifying detergent and cleaning products under the EU CLP Regulations without additional animal testing. The DetNet process helps and facilitates the access of smaller and medium-sized manufacturers to the market and ensures their competitiveness through enabling these companies to apply market conform product classifications although they have no or only little in-house toxicology data and experience. This is particularly important as most detergent mixture classifications are based on WoE analysis taking account of newly generated *in vitro* data and leverage on historical *in vivo* data without conducting new ones.

The DetNet process places a great emphasis on enabling its users to conduct and document state-of-the-art WoE mixture hazard and classification assessments. DetNet users are being supported through internal guidance documents in line with existing OECD guidance on integrated approaches and assessment (IATA) for skin irritation/corrosion[10] and serious eye damage or irritation.[15] These guidance documents describe the phases and elements of a WoE analysis and provide outlines of data matrices how a WoE assessment should be put together and transparently recorded. To ensure transparency of their WoE-based classification decisions, DetNet users are encouraged to attach WoE data matrices like those proposed by the OECD to their classification records.

Despite the QA processes in place, there are of course also issues and challenges with the DetNet database and process. One of them relates to the completeness of information available on the tested mixtures present in the DetNet database. Particularly the *in vivo* data have been mostly generated in the 1980's to end 1990's. During this time, the focus of the tested mixture characterisations was on analysing for quantity and type of surfactant content and other contributors to the irritation potential of the mixture (e.g., acidity/alkalinity; alcohols, solvent). Surfactants have not always been characterised in terms of chain length distributions or, where relevant, the ethoxylation degree in the same way it is done today. Minors that have been added to the mixtures for processing or aesthetic reasons (e.g., dyes, perfumes) at concentrations <1 % were often not reported with the consequence that the ingredients presented on the mixture data sharing format may be incomplete and/or not always add up to 100 %. Where existent, any uncertainties related to the nature and content of the ingredient in the tested mixture will need to be identified, considered and discussed in context of the mixture sameness analysis by the DetNet user to ensure transparency and increase the reproducibility of the assessment in case of an inspection.

Another, often criticised aspect relates to the fact that historically the detergent industry evaluated the eye irritation/corrosion potential of its mixtures predominantly in the rabbit LVET, a modification of the OECD TG 405 test method ('Draize test'). The difference between the two test protocols is that in the LVET only 0.01 ml of the test material (or corresponding weight for solids) is applied directly onto cornea while in the OECD TG 405 test method 0.1 ml of the test material (or corresponding weight for solids) is introduced in the conjunctival sac inside the lower lid. Industry's justification for these deviations from the standard protocol is based on anatomical and physiological consideration that the tear volume in both rabbit and human eyes is approximately the same. Moreover, the direct cornea exposure is considered to mimic more closely human exposure that can be expected following accidental ocular exposure to household detergents and cleaning products.

Due to the concern that the reduced exposure volume and different application procedure may result in a lower classification category (or no classification), existing ECHA guidance on the application of the CLP criteria requires a careful consideration of LVET data for eye hazard classification purposes. It only permits the use of LVET data as standalone method to justify an eye Category 1 classification. LVET data indicating an eye Category 2 or no classification should be viewed as not conclusive on its own.[16] The afore mentioned OECD guidance document on IATA for serious eye damage or irritation acknowledged by referring to[16,17] statements that retrospective LVET data may be useful on a case-by-case basis, for example in a Weight-of-Evidence approach, to identify potential ocular irritants for the limited use domain of detergent and cleaning products and their main ingredients. Accordingly, DetNet users are strongly advised against using LVET data on similar mixtures as standalone method in support of an eye Category 2 or no classification of an untested mixture. LVET data may only be used in this context along with other information relevant to the determination of the eye hazard classification of a mixture in a WoE approach as described in the OECD IATA for serious eye damage or irritation or the ECHA guidance on the application of the CLP criteria.

Lastly, it should be reiterated that the quality of classification decisions supported by DetNet depends on the knowledge and professional experience of the assessors using the tool about the chemical, physico-chemical and toxicological factors that may drive the skin and eye irritation/corrosion profile of detergent and cleaning products. Users should also be well acquainted with the underlying *in vitro* or vivo testing systems and scoring schemes to determine mixture's skin and eye hazards as well as the CLP provisions for the classification & labelling mixtures for hazardous properties. While the DetNet process incorporates several procedures and processes to ensure user eligibility and qualifications, the ultimate responsibility of the classification decision rests with the DetNet using Member Company. It is therefore also the

user's responsibility to stay abreast on any scientific or regulatory progress in the context of skin and eye hazard assessments of mixtures.

5 Conclusions

DetNet is the detergent industry's response to the challenges posed by the introduction of the EU CLP Regulation in 2008 and its final implementation for mixtures in 2015. Compared to the former EU Dangerous Preparations Directive, the lowering of the cut-off levels for mixtures containing skin and eye Category 1 classified ingredients, would have resulted in severe hazard classifications for most of the household detergents if the additivity rules were applied to determine the final mixture classifications, as is often done by manufacturers with limited in-house toxicological expertise. In most cases, the calculation-derived skin and eye hazard classifications do not reflect actual in-market experience with the hazardous properties of household detergents.

Anchored in Annex I of the CLP Regulation, DetNet is a voluntary initiative that promotes the sharing of data, expertise and best practices between manufacturers of detergent and cleaning products to support scientifically accurate and regulatory compliant product classifications. The DetNet process supports and facilitates the access of smaller and medium-sized manufacturers to the market and ensures their competitiveness by enabling them to apply market conform product classifications although these manufacturers have no or only little in-house toxicology data and experience. By leveraging on historical *in vivo* data and generating new *in vitro* data, DetNet further led to a simplified, reliable and harmonized way of classifying detergents and cleaning products for skin and eye effects without additional animal testing.

Scientifically, the concept behind DetNet has released substantial funding to support and establish the applicability domains of *in vitro* skin and eye irritation/corrosion testing systems for detergents and cleaning products. With increasing use and further expansion into more product categories, the challenge for the DetNet process will be to maintain the knowledge and professional experience of the DetNet users on the chemical, physico-chemical and toxicological factors that drive the skin and eye irritation/corrosion profile of detergents and cleaning products and the underlying test systems.

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