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Research article

SPECIFIC CONCENTRATION LIMIT AS A TOOL FOR CLASSIFYING MIXTURES BY HUMAN HEALTH HAZARDS. PART 1. CHARACTERISTICS, SCOPE, REGULATORY ASPECTS OF IMPLEMENTATION IN THE EAEU

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The Globally Harmonized System of Hazard Classification and Labeling of Chemicals (GHS) makes it possible to classify mixtures by hazardous properties using the calculation method and cut-off values/concentration limits (CV/CL). However, the CV/CL of hazardous components adopted in the GHS do not take into account their individual toxicological profile, which can lead to either underestimation or overestimation of the hazard posed by the entire mixture. To overcome these shortcomings of the GHS and to classify mixtures more accurately, specific concentration limits (SCL) are used along with CV/CL in the European Union (EU). The article presents: the characteristics and scope of SCL in accordance with the types of human health hazards included in the GHS, the possibility of setting numerical values of SCL higher than CV/CL, priority in their joint use and the mathematical criterion underlying the application of SCL. Example classification of model mixtures corrosive/irritative to skin based on SCL of their components is considered in a situation when the additive approach is applicable. The obtained results are compared with the classification based on the CV/CL without considering the SCL. Advantages and difficulties of SCL implementation in order to protect citizens from adverse effects of chemical factors while maintaining required production volumes in the chemical industry are discussed from the perspective of a mixture manufacturer and a regulatory authority. The author evaluated the possibility of SCL implementation for toxicological assessment of mixtures, considering the approved technical regulations of the EAEU «On the safety of chemical products» (TR EAEU 041/2017) and the standards that have come into force.

Keywords: *specific concentration limit, cut-off value, mixture, chemicals, classification, Globally Harmonized System of Classification and Labelling of Chemicals (GHS), technical regulation.*

The Globally Harmonized System of Hazard Classification and Labeling of Chemicals (GHS)[1] is the regulatory basis employed in many countries to regulate turnover of chemical products (CP) [1, 2]. An advantage of the GHS use is a possibility to classify mixtures by hazardous properties using relevant calculations[2]. However, the method adopted in the GHS does not take into account individual toxicological profiles of all mixture components, which can lead to either underestimation or overestimation of the hazard posed by the entire mixture [3–5].

An epidemic of allergic contact dermatitis can be a good example when underestimation has some serious consequences. It happened in the EU in 2010–2018 due to common use of a preservative methylisothiazolinone (CAS 220-239-6) in household chemicals, varnishes, paints and other chemical products [6–8] as well as in perfumes and cosmetics after consumers had refused from using paraben-containing products [9].

Since the mass fraction of methylisothiazolinone in CP was below 0.1 %, that is, below CV/CL established for the hazard class 1 skin

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[1] Globally Harmonized System of Classification and Labeling of Chemicals (GHS), 10th revised ed. New-York, Geneva, United Nations, 2023. Available at: https://unece.org/sites/default/files/2023-07/GHS%20Rev10e.pdf (February 09, 2025).

[2] State Standard GOST 32423-2013. Mixtures classification of hazard for health. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200108173 (February 09, 2025) (in Russian).

sensitizers, these chemical products were not classified using the calculation method as posing such health threats; in reality, they often caused allergic reactions [10].

Since izothiazolinones have sensitizing effects in levels substantially lower than CV/CL [11], the break of the foregoing epidemics called for stricter legal rules of their use. In particular, SCL equal to 0.0015 %[3] was fixed for methylisothiazolinone, that is, 66 times lower than CV/CL. This chemical was prohibited for use in leave-on perfumes and cosmetics[4], and its permissible mass fraction in rinse-off products was lowered from 0.01 % to SCL[5]. The taken measures reduced manifestation frequency of allergic contact dermatitis to methylisothiazolinone [12].

An example when hazard was overestimated is classification of acid- and base-containing mixtures using CV/CL equal to 1 % for the hazard class 1 per such indicators as skin irritation / corrosion and eye damage / irritation in a situation when the additive approach is not applied. Actually, many strong acids and bases produce corrosive effects on skin and eyes in considerably higher concentrations in spite of extreme pH values [3, 13, 14].

The aim of this study was to describe a method for classifying chemical mixtures per their health hazardous properties, which is adopted in the EU and based on using SCL; to estimate its advantages and difficulties in using it as well as a possibility to implement it in the EAEU. Methods for SCL identification will be described in a separate article.

SCL description and field of application. According to the definition[6], specific concentration limit (SCL) is a limit assigned to a substance indicating a threshold at or above which the presence of that substance in a mixture leads to the classification of this mixture as hazardous.

It should be noted that SCL are commonly used only in the EU whereas such practices are much less frequent in, for example, the USA or Canada although valid regulatory documents in these countries allow using concentration limits different from CV/CL to classify CP[7].

The EU legislation[6] stipulates the following conditions for SCL use:

– SCL is established by CP manufacturers, importers or downstream consumers (users);

– SCL is eligible for both physical threats and human health hazards;

– since several hazard classes are applied for many hazard types, SCL can be both one-sided ($C \geq 5.5$ %) and two-sided ($0.5\ \% > C \geq 2$ %) similar to CV/CL established in the GHS;

– SCL, just like CV/CL, is established in mass fractions for liquid and solid mixtures and in volume fractions for gaseous ones;

– SCL has a priority over CV/CL when a mixture is classified;

– SCL can be both higher and lower than CV/CL [15].

It is specifically noted that SCL can be higher than CV/CL in exceptional cases only

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[3] Comission Regulation (EU) 2018/1480 of 4 October 2018 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures and correcting Commission Regulation (EU) 2017/776. *OJEU*, 2018, Ser L, vol. 61, no. L251, pp. 1–12. Available at: http://data.europa.eu/eli/reg/2018/1480/oj (February 09, 2025).

[4] Commission Regulation (EU) 2016/1198 of 22 July 2016 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. *OJEU*, 2016, Ser L, vol. 59, no. L198, pp. 10–12. Available at: http://data.europa.eu/eli/reg/2016/1198/oj (February 09, 2025).

[5] Commission Regulation (EU) 2017/1224 of 6 July 2017 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. *OJEU*, 2017, Ser L, vol. 60, no. L174, pp. 16–18. Available at: http://data.europa.eu/eli/reg/2017/1224/oj (February 09, 2025).

[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *Publications Office of the European Union*. Available at: http://publications.europa.eu/resource/cellar/c6b6a31d-8359-11ee-99ba-01aa75ed71a1.0004.02/DOC_2 (February 09, 2025).

[7] Sullivan K. Can the European Union's specific concentration limits for skin sensitization be used in the United States and Canada? *SCHC Spring Meeting*, 2019. Available at: https://www.knoell.com/en/news/eus-specific-concentration-limits-for-skin-sensitization-use-in-the-us-and-canada (February 09, 2025).

when there is reliable and convincing evidence that a hazard posed by a component in a mixture does not manifest itself in concentrations below SCL.

Since SCL identification requires additional efforts to conduct a toxicological assessment, such limits have been established for few types of chemicals[6]. The author believes that cases when solid grounds are provided for establishing SCL above CV/CL will cease to be a rare exception as new data will be accumulated on hazardous properties of chemicals in future.

SCLs are mentioned in the EU harmonized classification of chemicals[6]; possibility of their use depends on a hazard type and class[8].

SCLs are never used to classify mixtures per acute toxicity or aspiration hazards. SCLs can be fixed both above and below CV/CL for all hazard classes as regards skin irritation / corrosion, serious eye damage / irritation, skin and respiratory sensitization, mutagenic effects on embryo cells, carcinogenic effects and reproductive toxicity. Possibility to use SCL for specific toxicity as regards target organs (both upon single and repeated exposure) depends on a hazard class. SCL can be only below CV/CL for the hazard class 1; SCL is not applicable for the hazard class 2: SCLs can be fixed both above and below CV/CL for the hazard class 3 (toxicity upon repeated exposure).

In case components in a mixture are of the same type and have the same hazard class, and SCLs are established for n out of them whereas only CV/CKL are established for m out of them, such a mixture is classified by determining the sum (1) if the additive approach is applicable[8]:

$$\sum_{i=1}^{m}\frac{C_i}{CV/CL_i}+\sum_{j=1}^{n}\frac{C_j}{SCL_j}, \qquad (1)$$

where C_i (C_j) is the mass (volume) fraction of the i (j) component in the mixture, %.

In case the sum (1) is equal to or above 1, the whole mixture is assigned the hazard class, which corresponds to the hazard class of its components. Otherwise, a similar calculation is performed for a lower hazard class.

Examples of using SCL for mixture classification. Let us consider some examples when model mixtures 1-3 are classified per the hazard type 'skin irritation / corrosion' using SCL within the additive approach. Their relevance results from significance of this health hazard [16] and a considerable proportion of additive effects between toxicants that pose it [17].

Compositions of the mixtures and SCL for their components are given in Table 1–3. To reduce the number of examples, we assume that the analyzed mixture components, chemicals A–F, have the hazard class 1. CV/CL for such components equal to $C \geq 5$ % for the hazard class 1 and $1\ \% \leq C < 5$ % for the hazard class 2 in conformity with the GHS.

Table 1

Initial data for classifying the mixture 1

Mixture component	Mass fraction, %	SCL, %	
		For class 1	For class 2
A	3	$C \geq 7$	$1 \leq C < 7$
B	5	$C \geq 10$	$3 \leq C < 10$
Water	92	-	-

Table 2

Initial data for classifying the mixture 2

Mixture component	Mass fraction, %	SCL, %	
		For class 1	For class 2
C	2	$C \geq 1$	$0.5 \leq C < 1$
D	1.5	$C \geq 2$	$1 \leq C < 2$
Water	96.5	-	-

Table 3

Initial data for classifying the mixture 3

Mixture component	Mass fraction, %	SCL, %	
		For class 1	For class 2
E	4	$C \geq 8$	$2 \leq C < 8$
F	3	Not available	Not available
Water	93	-	-

[8] Guidance on the Application of the CLP Criteria. Part 1: General Principles for Classification and Labelling. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. *European Chemicals Agency*, 2024, Version 5.0, 55 p. Available at: https://echa.europa.eu/documents/10162/2324906/clp_part1_en.pdf/bc58ea9e-2e72-732e-2d34-5d34180ec33f (February 09, 2025).

The following sums are to be calculated for classifying the mixture 1 using SCL:

– for the hazard class 1: $3/7 + 5/10 = 0.43 + 0.50 = 0.93 < 1$;

– for the hazard class 2: $3/1 + 5/3 = 3.00 + 1.67 = 4.67 \geq 1$.

Therefore, taking SCL into account allows giving the hazard class 2 to the mixture 1. In total, the mass fractions of the components with the hazard class 1 are 3 % + 5 % = 8 %, which is above CV/CL established by the GHS for this hazard class where they equal 5 %. Consequently, if we are guided only by CV/CVL, we should assign the hazard class 1 to the mixture 1.

For the mixture 2, calculating the sum (1) using SCL for the hazard class 1 yields the following result: $2/1 + 1.5/2 = 2.00 + 0.75 = 2.75 \geq 1$, which means the mixture should be assigned the hazard class 1.

In total, the mass fractions of the components with the hazard class 1 are 2 % + 1.5 % = 3.5 %, which is below CV/CL for the hazard class 1, equaling 5 %, but above CV/CL for the hazard class 2, equaling 1 %. Consequently, if we are guided only by CV/CVL, we should assign the hazard class 2 to the mixture 2.

The foregoing examples show the situations when SCL is not taken into account and this leads to both overestimating hazard posed by a mixture (the mixture 1) and underestimating them (the mixture 2).

The example of the mixture 3 describes a situation how to use SCL in case it has not been established for each component in it.

Since there is no SCL established for the component F in the mixture, the established CV/CL are used in calculating the sum (1). The results are $4/8 + 3/5 = 0.50 + 0.60 = 1.10 \geq 1$ for the hazard class 1. Therefore, this hazard class can be assigned to the mixture 3.

Using SCL: advantages and difficulties. The author believes that SCL use for classifying mixtures is interesting both from the point of view of manufacturers who produce chemical products and regulatory authorities as well.

In case SCL is higher than CV/CL, a concentration of a component in a mixture can be increased quite safely and, accordingly, volumes of production involving use of this component and the mixture as whole. This will have a positive effect on financial state of chemical manufacturers.

Establishing SCL lower than CV/CL makes it possible to protect a large number of consumers from health hazards posed by a mixture, reduce a number of poisonings and potential legal actions associated with health harm to downstream consumers as well as reputation losses borne by a manufacturer and a regulatory authority who permitted this mixture to be marketed.

Certain difficulties involved in implementing SCL include the necessity to determine their numeric values and to develop relevant methods for doing it. SCL establishing increases costs borne by CP manufacturers; however, first of all, they can be compensated for by expanding a sphere where a chemical product is allowed for application and by increasing production volumes. Secondly, these costs can be distributed between, for example, manufacturers who supply components and who produce end mixtures within joint notification of a chemical or registration of a mixture.

Using SCL together with CV/CL makes the mixture classification procedure more complicated, which requires additional training for personnel who deal with it. However, classification can be automated by using relevant software; some simplest calculators can be found online[9].

Evident significance of using SCL in regulation has been described above. In addition, SCL allow more precise classification of mixtures by calculations, which makes for a decline in CP manufacturers' costs since additional testing using *in vivo* methods is no longer required. At the same time, a reduction in the number of animals used for tests is widely appreciated due to not only some humanistic concerns [18] but also difficulties in

[9] Khrolenko M. Online mixture classification calculator. Available at: https://mixclass.net (February 09, 2025).

planning up-to-date toxicological experiments. The latter require strict control and consideration of many factors, which can involve accidental or systemic errors [19] as probable reasons for differences in toxicometric indicators published by different research teams.

However, it is objectively difficult to quantify advantages of using SCL as regards more precise classification since this requires free access to a database containing many mixtures, which have been estimated by using two foregoing methods. Calculated classification in such a database should be represented by two values, one of them obtained by using SCL and the other without it. Bearing in mind that SCLs are not established for every chemical, as well as the fact that exact compositions of mixtures are, as a rule, unknown due to protection of commercially significant information, wide validation of the SCL concept has not been accomplished so far.

A study [20] rather indirectly assesses SCL advantages as it comparatively analyzes the classification results obtained for plant protection products by using calculations and animal tests. Satisfactory coincidence of identified hazard classes was established for skin irritation / corrosion (the proportion of false negative results, that is hazard underestimation, is 22 %) and eyes irrigation / damage (the proportion of false positive results is 66 %); unsatisfactory results were obtained for skin sensitization (the proportion of false negative results is 34 %). The latter might be due to high CV/CL established in the EU for the hazard classes 1 and 1B per skin sensitization, namely 1 % (mass fraction). It is noteworthy that a similar proportion of false negative results was obtained by using *in vitro* methods. Unfortunately, the study does not provide any information about frequency of using SCL when performing classification by calculations. This does not allow using this and similar studies [3–5] to the full to estimate advantages of using the SCL concept when classifying a wide range of chemical products.

Regulatory and legal aspects of SCL implementation in the EAEU. At present, the valid standards used in the EAEU to classify CP[10] do not involve using SCL. Therefore, SCL implementation requires alterations made in these standards or development of new ones.

It is also noteworthy that the system comprising hazard classes of chemical products and CV/CL adopted within it in the EU[11], where SCL is commonly used for mixture classification, is very different from a system adopted in the EAEU [21]. These differences make it impossible to automatically transfer elements of CP regulation based on using SCL in the EU in regulation of chemical products adopted in the EAEU.

Although a possibility to use SCL is not mentioned in any valid standards and Technical Regulations of the EAEU 041/2017[10], the author believes that the existing regulatory-legal base allows implementing them into CP regulation.

First of all, EAEU TR 041/2017 is based on the GHS, which stipulates that hazardous properties of a component in a mixture can manifest themselves in a concentration both higher and lower than its CV/CL[12].

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[10] State Standard GOST 32423-2013. Mixtures classification of hazard for health. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200108173 (February 09, 2025) (in Russian); EAEU TR 041/2017. O bezopasnosti khimicheskoi produktsii: Tekhnicheskii reglament Evraziiskogo ekonomicheskogo soyuza, Prinyat Resheniem Soveta Evraziiskoi ekonomicheskoi komissii ot 3 marta 2017 g № 19 [On Safety of Chemical Products: Technical Regulations of the Eurasian Economic Union, approved by the Council of the Eurasian Economic Commission on March 3, 2017 No. 19]. *Information and legal system of regulatory and legal acts of the Republic of Kazakhstan*. Available at: https://adilet.zan.kz/rus/docs/H17EV000019 (February 10, 2025) (in Russian).

[11] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *Publications Office of the European Union*. Available at: http://publications.europa.eu/resource/cellar/c6b6a31d-8359-11ee-99ba-01aa75ed71a1.0004.02/DOC_2 (February 09, 2025).

[12] Globally Harmonized System of Classification and Labeling of Chemicals (GHS), 10th revised ed. New-York, Geneva, United Nations, 2023. Available at: https://unece.org/sites/default/files/2023-07/GHS%20Rev10e.pdf (February 09, 2025).

Secondly, certain SCLs are planned to be introduced in the EAEU by approving the List of Chemicals with Carcinogenic and Mutagenic Effects, Reproductive Toxicity, and Chronic Toxicity for Water Environment as Appendix to the Procedure for Creating and Keeping the Register of Chemicals and Mixtures of the Eurasian Economic Union[13]. Thus, for example, this List establishes SCL for benzo(a)pyrene (carcinogenic, hazard class 1A) as equal to 0.005 %, which is 20 times lower than its CV/CL.

Third, after TR EAEU 041/2017 comes into force, CP toxicological assessment aimed at creating safety profiles and subsequent state registration will make it possible to use information about chemicals, which has already been accumulated by the humankind and is available in various databases. A draft of the Procedure for Creating and Keeping the Register of Chemicals and Mixtures of the Eurasian Economic Union[13] already envisages the possibility to use EU databases containing information about SCL. Bearing this in mind, we can state that numeric SCL values, which can be found in them, are actually legalized in the EAEU.

In case SCLs are implemented, the Appendix No. 4 to the EAEU TR 041/2017 will need revising. Since SCL covers such hazards as mutagenicity, carcinogenicity and reproductive toxicity, stricter control of mixtures that contain carcinogens, mutagens and reproductive toxicants will rely on using not their CV/CL enlisted in this Appendix but their SCL instead.

Conclusions:

1. CV/CL use for mixture classification can both overestimate and underestimate their hazard.

2. SCL allows classifying mixtures more precisely using the calculation method and thereby optimizing their use as regards both protecting downstream consumers from their adverse effects and increasing volumes of CP production.

3. SCL implementation for mixture classification will require making certain alterations in the EAEU legislation, revising the existing standards and (or) developing new ones, which can provide relevant algorithms for using the calculation method within toxicological assessment of mixtures considering the sum (1).

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