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Classification of the liquid products (e-liquids) which contain nicotine based on the regulation 1272/2008/WE (CLP) including the scientifically proven test results of the nicotine (CAS 54-11-5)

Nicotine is found in the annex VI of the regulation CLP (1272/2008/WE) and has harmonised classification:

Classification of the nicotine acc. to directive 67/548/EWG:	T+ R27, T R25, N R51/53
Classification of the nicotine acc. to 1272/2008/WE:	Acute Tox. 1 H310, Acute Tox. 3 (*) H301, Aquatic Chronic 2 H411

Wherein:

- **R27 Affects very toxically while contact with skin**, which is an equivalent of *LD50 (skin, rat or rabbit) below or equal 50 mg/kg body weight*.
- **R25 Affects toxically while swallowed**, which is an equivalent of *LD50 (orally, rat) over 25 to 200 mg/kg body weight*.
- **Acute Tox. 1 H310 Could be fatal while contact with skin**, which is an equivalent of *LD50 (skin, rat or rabbit) below or equal 50 mg/kg*.
- **Acute Tox. 3 H301 Affects toxically while swallowed**, which is an equivalent of *LD50 (orally, rat) over 50 to 300 mg/kg body weight*

(*) At some hazard classes including acute toxicity, the classification acc. to directive criteria 67/548/EWG does not correspond directly to the classification under classes and categories danger by virtue of present ordinance. In such cases classification given in the table 3.1 should be treated as the minimum of classification.

If a producer or importer has an access to the given or different information, which leads to classify in the category of higher danger than minimum then the classification of such a higher category should be used.

If we use the possibility of increasing the classification then we obtain a class and category danger

- **Acute Tox. 2 H300 Swallowing could be fatal**, which corresponds to *LD50 (orally, rat) over 5 to 50 mg/kg body weight*

Assigning the acute toxicity to a liquid is done on different principles acc. to CLP ordinance and different principles of directive of preparation (1999/45/WE). Acc. to directive of preparation for a calculation we take into account the percentage of the given component. Otherwise, while classifying the liquids because of acute toxicity acc. to regulations of ordinance of CLP should be used the formula included in the section 3.1.3.6.1, basing on which we can calculate the estimated value of acute toxicity (ATE

mix), which is further compared with the numerals criteria presented in the table 3.1.1 (ordinance CLP).

Value ATE for a liquid is appointed on the base of:

- value LD50/CL50, if there are known

or

- suitable conversion factor presented in 3.1.2 annex. I to the ordinance CLP.

There is a number of reliable (confirming harmonised classification) and update results of the toxicity tests of the nicotine described in the scientific literature, which should be successfully used for creating the classification of e-liquids. They are as follows:

- LD50 (orally, rat) 50 mg/kg (Farm Chemicals Handbook. Vol. -, Pg. C219, 1991)
- LD50 (orally, rat) 50 mg/kg (Sine C, 1993)
- LD50 (orally, rat) 50-60 mg/kg (Trochimowicz HJ, Kennedy GL Jr, Krivanek ND (1994). Heterocyclic and miscellaneous nitrogen compounds. Clayton GD, Glayton FE, ed. Patty's Industrial Hygiene and Toxicology, 4th ed. John Wiley&Sons, Inc. New York, IIE, 3374-3379, 3489-3491)
- LD50 (orally, rat) 70-71 mg/kg (Yam J, Reer PJ, Bruce RD (1991).)
- LD50 (skin, rabbit) 50 mg/kg (Quarterly Bulletin--Association of Food and Drug Officials of the United States. Vol. 16, Pg. 3, 1952.)
- LD50 (skin, rat) 140 mg/kg (World Review of Pest Control. Vol. 9, Pg. 119, 1970.)
- LD50 (skin, rat) 140 mg/kg (Trochimowicz HJ, Kennedy GL Jr, Krivanek ND (1994). Heterocyclic and miscellaneous nitrogen compounds. Clayton GD, Glayton FE, ed. Patty's Industrial Hygiene and Toxicology, 4th ed. John Wiley&Sons, Inc. New York, IIE, 3374-3379, 3489-3491)
- LD50 (skin, rat) 285 mg/kg (Handbook of pesticide toxicology (1991) [Red.] W.J. Hayes. Vol. 2. New York, Academic Press, 603-608)

DIGESTIVE TRACK

Values LD50 (where the tested organisms were rats) for the nicotine, published over time, are included in the range from 50 to 188 mg/kg body weight, from which the majority of values is located from 50 to 83 mg/kg body weight. (publications 1969-2004).

Acc. to ordinance 1272/2008 „Preferred species, on which the acute toxicity tests should be conducted while using digestive track and after inhalation are rats. While testing acute toxicity in contact with skin this should be conducted on rabbits or rats.”

Taking into account the established by eu experts classifications of the nicotine it should be taken that the value LD50, which is used for classification will be included in the range 50-300 mg/kg body weight.

That is why, for calculating the classification after swallowing of liquids which contain nicotine were considered into account the research LD50 (orally, rat) 50 mg/kg, which are equal the upper limit of the range in the category 2.

SKIN

While doing tests on rats there can be found in the literature the values which range from 140 to 285 mg/kg body weight (Publications 1960 and 1994). Value 50 mg/kg were obtained while doing tests on rabbits, which seem to be more prone to the nicotine effect (publications: Trochimowicz HJ, Kennedy GL Jr, Krivanek ND (1994)).

While classification the acute toxicity on skin only the value of tests on rabbits are placed in the range which corresponds to the proposed by eu experts classification as Acute Tox. 1 H310. The rest values are do not fit in the scope of classification of the danger category.

Taking the above assumptions from ordinance CLP, to calculate the classification after having contact with skin of liquids which contain nicotine were taken into account the research LD50 (skin, rabbit) 50 mg/kg.

CONCLUSIONS

With reference to all above, in order to calculate to values ATEmix of liquids we can take into account the above mentioned researches because they fulfil the all crucial research criteria, which are discussed in 1272/2008/WE, namely:

- they had been conducted on species described by CLP ordination as preferred,
- are placed in the subject literature, in the approved scientific journals, so they arrived from the trusted source and are reliable data,
- the values published there confirm the harmonized classification placed in the annex VI of the CLP ordination.

This study was prepared as a need to support e-liquids classification containing the nicotine (CAS 54-11-5).