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Response to consultation on CLH report for harmonised classification of Propane-1,2-diol under STOT-SE 3, respiratory tract irritant.

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1. Refers to Part A, 2.1 & 2.4 of CLH dossier

From a total of 4966 C&L notifications submitted to ECHA, only 10 notifications (0.20%) reported a self-classification of STOT-SE-3. From these 10 notifications, 8 assigned it H335 *(May cause respiratory irritation)* and 2 notifications assigned it H336 *(May cause drowsiness or dizziness)*. Moreover, none of these notifications (except for 3) identified a specific target organ and all of them provided no specific reasons for classification into STOT-SE-3 categories.

Thus, it can be concluded that from all the self-classification, a negligible number of applications classified propylene glycol for STOT-SE-3 category.

2. Refers to Part A, 2.2 of CLH dossier

a) The reference **(gutefreg.net, 2012)** provided in support of the statement, "In other internet chats the potential to harm by its use as theatrical fog is discussed" does not mention/discuss significant harm to the respiratory track or lungs. In fact, the only statement in the chat that could be attributed to discussing "potential to harm" to respiratory system is "Allerdings wirkt Propylenglykol reizend, insbesondere auf Schleim- und Bindehäute. In gasförmiger Form kann so etwas hauptsächlich Sängern Probleme bereiten, in flüssiger Form hingegen ist die Reizwirkung wohl recht stark, Kontakt mit dem Nebelfluid selbst sollte man also vermeiden." This roughly translates to: "However, propylene glycol is an irritant, and in particular to mucous and conjunctiva. In gaseous form, it may mainly pose problem to singers; in liquid form, however, the irritation is probably pretty strong but it is hard to get in contact with the smoke fluid itself so you should avoid."

b) The authors of the dossier report that "there are numerous reports on irritation and sore throat in internet forums when propane-1,2-diol was used as liquid in electronic cigarette." This statement is then supported by a reference **(Federal office of public health (BAG), Switzerland)**. This referenced web article in fact discusses the use of prpane-1,2-diol in traditional tobacco cigarettes, as opposed to electronic cigarettes as the author(s) of dossier seem to be referring to. Moreover, the article discusses the formation of other harmful chemicals when propylene glycol is burnt along with the tobacco in the cigarette.

Thus, it can be concluded that the authors of the dossier have, perhaps, misunderstood the referenced articles and have made misleading inferences.

3. Refers to part 4.3 and 4.3.1 of CLH dossier

The key human study **(Wieslander *et al.*, 2001)** used in the dossier to support proposed CLP classification has some key limitations. The sample size of the study was only 27 human volunteers. From this population, a significant proportion had a history of atopy, hay fever and childhood eczema *(total 60%, may not be mutually exclusive)* indicating that these subjects may already be sensitive or susceptible to irritation or inflammation. Apart from the lung function test, all other results obtained during the study were subjective. The tear film stability test was not performed using fluoresceine or any other technique that is regularly used for clinical diagnosis or research and instead relied on self-reported subjective endpoint of the subjects where the breakup time was taken as "the time the subject could keep the eyes open without pain, when watching a fixed point at the wall". Although this primitive method has been used in 3-4 research studies (including one from the same research group) and a correlation has been shown with the fluoresceine method, it is not widely accepted method of measuring or estimating the tear film breakup time. Moreover, a tear film breakup time is not a good and reliable test for assessing ocular irritation and is generally used to diagnose dry eyes. A relatively recent review article demonstrates very well the difficulties with measuring tear film stability and what different factors can affect it **(Sweeney *et al.*, 2013)**. It is likely that there are many factors that may have influenced this self-reported subjective endpoint for tear film measurement and thus the results cannot be considered conclusive for inference that propylene glycol can induce ocular irritation. What is more interesting is that propylene glycol is used in at least one of the commercially available eye drop brands that are used for treatment of dry eyes (Systane Lubricant Eye Drops; Alcon, Fort Worth, TX) and one study **(George *et al.*, 2007)** found it to be significantly more effective in prolonging tear film breakup time and improved ocular protection index when compared to two brands of eye drops that did not contain propylene glycol.

The only objective study included in the research was lung function test using dynamic spirometry. However, this test was performed without a nose clip and the results obtained from these tests were not significantly different before and after exposure to propylene glycol mist. Although the CLH dossier submitters report in section 4.3.1 that after the exposure to PG mist, the forced expiratory volume in one second (FEV_1) was slightly reduced, this reduction was insignificant with the value decreasing from 4.01 to 3.98 with standard deviations of 0.71 and 0.78 respectively ($p = 0.29$). The dossier submitter also report that "four subjects reacted with irritative cough, mild airway obstruction, and mild dyspnoea". However, as highlighted earlier, a significant number of subjects had a history of atopy, hay fever and childhood eczema and thus these may already be susceptible or sensitive to respiratory or other irritation.

One more important factor to note here is that all the subjects recruited in the study were naïve, in that none had previous exposure to propylene glycol and thus it could be argued that some of the effects reported in the self-administered questionnaire

could be due to adaptive responses. This phenomenon has been observed among users of electronic cigarette containing propylene glycol, where the initial use of these devices causes throat irritation and cough in some of the users but these symptoms disappear after two to three days of usage. The very same users are able to continue using these devices regularly without reporting any such symptoms or effects.

Thus, it can be concluded that the key human study used in support of the proposed CLP classification has many limitations and is not a reliable study for justifying such classification of propylene glycol, viz. STOT-SE 3 for respiratory tract irritation. No data from this key study (even with restrictions) directly supports the notion that propylene glycol may be responsible for respiratory tract irritation and does not justify such CLP classifications.

4. Refers to part 4.3.2 of CLH dossier

a) The limitations of the key human study used in support of the proposed classification have already been highlighted above. Considering that fact that a major proportion of the study population had a history of atopy, hay fever, childhood eczema, and consisted of smokers and ex-smokers, it cannot be said with certainty whether the symptoms reported could be due to isolated idiosyncratic reactions or whether the results obtained are representative of the effects that would be observed in a wider population. It is interesting to note that although 61% of volunteers reported throat dryness and 16% reported symptoms suggestive of impaired respiratory function, none reported difficulties in breathing. The original authors of the study **(Wiselander *et al*., 2001)** report that "the most common symptoms were a sensation of sore and dry eyes, throat dryness, and irritative cough", and none of these symptoms are statistically significant (except dry throat) unless they are grouped for various organs. Even when symptoms are grouped for a particular organ, the results are statistically significant for only ocular and throat symptoms where as they remain statistically insignificant for nasal, lower respiratory, general and dermal symptoms.

   Thus, even though the dossier submitter suggests that the results reported in the key human study are suggestive of respiratory irritant effects and thus satisfy 3.8.2.2.1.(a) of the CLP criteria, a careful evaluation of the study reveals otherwise.

b) As mentioned earlier, the decrease in the FEV_1 (as reported in Wiselander *et al*., 2001 study) was marginally low and this decrease was statistically insignificant *($p = 0.29$)*. Moreover, the lung function test by dynamic rhinometry was performed without a nose clip. The lung function test itself is well known to have a large deviation from normal value and a decrease FEV_1 is not a clear indicator of the respiratory tract irritation. Thus, conclusion of the dossier submitter that this slight decrease in FEV_1 is indicative of impaired lung function is unsubstantiated and misleading. Thus, the arguments used in the dossier in support of 3.8.2.2.1.(b) of the CLP criteria is invalid and does not satisfy this criterion.

c) There were a significant number of volunteers who could have sensitive airways owing to their history of atopy, hay fever or childhood eczema (none of the subjects, however, were not diagnosed asthmatic by a physician). Moreover, all the volunteers were naïve in that they were never exposed to propylene glycol at a workplace and thus many of the symptoms reported could be attributed to the adaptive or reflex response as it is observed among first time electronic cigarette users. The population size was also smaller (27 volunteers) and the study was not a blind study. All of the results used for drawing conclusions were obtained by subjective questionnaire and the only objective observation was lung function test which revealed no important differences after exposure to propylene glycol. Thus, the dossier submitters' conclusion that the Wiselander *et al*., 2001 study satisfies 3.8.2.2.1.(c) of the CLP criteria is inaccurate.

Thus, it can be concluded that there is a lack of reliable human study (with or without limitations) that indicate that propylene glycol can be classified under STOT-SE, category 3 for respiratory tract irritation. Also, there is no study that report consistent and identifiable toxic effects in humans when exposed to propylene glycol as required by 3.8.1.3 of the CLP classification criteria.

5. Other reports

The dossier submitters do not seem to have taken into consideration other reports related to propylene glycol that suggest that it does not pose any significant risk to the human health and that it does not require classification under STOT-SE, category 3 for respiratory tract irritation. Some of these reports include **Corcoran *et al*., 2014; Niven *et al*., 2011; Burkart *et al.*, 2003; and Wang *et al*., 2007.** Lastly, electronic cigarette users (millions of them) are regularly exposed to propylene glycol via inhalation that is aerosolised using vaporisers and there have been no reports of respiratory irritation among majority (if not all) of these users. In fact, the numbers of electronic cigarette users are constantly on the rise and they seem to have no irritative response to propylene glycol smoke.

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