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Final

Propylene Oxide and Propylene Glycols REACH Consortium Response to ECHA March 8, 2016 Notification of CLH report Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 Substance Name: Propane-1,2-diol (EC Number: 200-338-0)(CAS Number: 57-55-6). Dossier submitted by BAuA, October 2015.

Summary: The available information does not support the proposed H335 CLH classification of propane-1,2-diol (propylene glycol) as a respiratory irritant. Overall, the currently available evidence is not convincing for propylene glycol as causative for respiratory tract irritation. The existing data for humans and animals is very limited, the reported findings weak and do not rise to the level of classifiable effects. Most of the human data is based on exposures to mixtures of substances and hence cannot inform on any associations between propylene glycol and respiratory irritation. Only one study evaluated exposures to propylene glycol alone, however, the study's findings do not demonstrate respiratory irritation effects. Importantly, the study's objective measurements showed a small change well within the normal variation expected for this type of repeated spirometric measurements that does not indicate adverse respiratory effects. The reported subjective symptoms of throat and ocular dryness also do not support the classification of respiratory irritation as, according to ECHA's CLP guidelines, these are not considered relevant sensations. The animal data likewise only indicate mild clinical and mucosal changes that are not hallmarks of irritation responses. There are no credible histopathology reports in the animal studies that document propylene glycol-induced cytotoxicity or inflammation in the respiratory tract of inhalation-exposed laboratory animals. The findings that are reported were limited to exposure-related increases in the amounts of nasal epithelial mucus, but without evidence of any associated inflammatory cell response in the nasal mucosa. Without evidence of concurrent or preceding inflammation or epithelial cytotoxicity (cell death or degeneration), this single mucus morphologic finding does not warrant a label of irritancy for propylene glycol at these levels of exposure. The effects reported for propylene glycol in humans and animals do not indicate irritation responses and more likely are indirect effects of the local drying of the airway mucosa due to the hygroscopic nature of this substance. These effects are not harmful or adverse and rather are adaptive to the minor physiological change. Given these reports and questionable findings, the major European producers of propylene glycol have committed to improve the information on human respiratory irritation with a new study. Due to the absence of data supporting safe use of propylene glycol for artificial smoke and electronic cigarettes, the major European producers of propylene glycol do not support and advise against these uses.

Below, please find detailed arguments, based on the summary, that are arranged in the following sections:

1. The available scientific information does not support propylene glycol causing respiratory irritation.

1.1 The available human data do not support the classification of propylene glycol as a respiratory irritant.

The proposed H335 classification of propylene glycol as a respiratory irritant is reportedly justified based on the findings of four studies conducted in humans, three of which involve exposures to multiple other compounds, including propylene glycol. However, analysis of these studies indicates that there is insufficient human scientific evidence presented to classify propylene glycol as a respiratory irritant.

The specific guidance document that is used to classify substances as respiratory tract irritants requires that the evaluation of human data is based on, (1) experience from occupational exposure, (2) published data on volunteers (including objective measurements, psychophysical methods and subjective reports and (3) other data such as from nasal lavage. The effects required to substantiate respiratory irritation are stated as: localized redness, oedema, pruritis and/or pain and functional impairments such as cough, pain, choking and breathing difficulties (European Chemicals Agency, 2015).

Four studies were cited as providing evidence for respiratory irritation:

Burr, G.A., Van Gilder, T.J., Trout, D.B., Wilcox, T.G. and Driscoll, R. (1994). Health Hazard Evaluation. HETA 90-0355-2449. http://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0355-2449.pdf

Moline, J.M., Golden, A.L., Highland, J.H., Wilmarth, K.R. and Kao, A.S. (2000). Health effects of evaluation of theatrical smoke, haze and pyrotechnics. Equity-League Pension and Health Trust Funds.

Wieslander, G. and Norbäck, D. (2010). Ocular symptoms, tear film stability, nasal patency and biomarkers in nasal lavage in indoor painters in relation to emissions from water-based paints. International Archives of Occupational and Environmental Health. 83: 733-741.

Wieslander, G., Norbäck, D. and Lindgren, T. (2001). Experimental exposure to propylene glycol mist in aviation emergency training; acute ocular and respiratory effects. Occupational and Environmental Medicine. 58:649-655.

Of the four studies cited, only one (Wieslander et al., 2001) is capable of associating any observed effects with propylene glycol exposure.

The NIOSH study (Burr et al.,1994) evaluated symptom reports among actors in Broadway productions who were exposed to a variety of glycol compounds in addition to propylene glycol, including ethylene glycol, 1,3-butylene glycol, diethylene glycol and triethylene

glycol. Ethylene glycol, in particular, has been shown to be a respiratory irritant (Wills et al., 1974), although at higher concentrations than those measured in this study.

The Moline et al. (2000) study also evaluated exposure to mixed glycols, including butylene, diethylene, triethylene and propylene glycol. No significant acute change in voice quality, pulmonary function, or vocal cord appearance was found. Although actors with exposures to elevated or peak levels of glycols reported more symptoms than actors with less exposure, the mixed nature of the exposures makes it impossible to identify any symptoms as being due to propylene glycol exposure.

The Wieslander and Norbäck (2010) study evaluated exposure of painters to a water-based paint that included propylene glycol among other glycol compounds and other volatile organic compounds. The authors concluded that the increase in eosinophilic cationic protein (ECP) obtained from nasal lavage was indicative of airway irritation. However, it is impossible to attribute the association between propylene glycol and ECP. As the CLH report acknowledges, 'due to the mixed exposures to different components emitted from the water-based paints, the findings cannot be associated with propylene glycol as the only origin of irritative effects on the eyes and nasal mucosa'.

The key study that the CLH report relies upon for classification of propylene glycol as a respiratory irritant is the Wieslander et al. (2001) study. This study evaluated subjective symptom reports, and two measures of putative respiratory irritant response: pulmonary function and nasal resistance. The CLH report concluded that this study fulfilled the criteria for respiratory irritant effects because it demonstrated that mild airway obstruction produced impaired function of the lower respiratory tract. The data, however, suggest otherwise. There was a 1% change in FEV1, post-exposure, which is neither statistically or clinically significant, especially since post-exposure values were 102% of predicted for this healthy cohort. The small, albeit significant, decrease in the FEV1/FVC ratio is also not indicative of impairment of lower airways as the ratio was greater than 80% both pre- and post-exposure, indicating an absence of any obstructive defect (American Thoracic Society, 2005).

<u>A 5% decrease in FEV_1, shown by only 4 out of 27 volunteers, cannot be considered significant or indicative of lung impairment due to exposure to a respiratory irritant, as this decrease is well within the normal variation expected with repeated spirometric measurements.</u> The testing and, most importantly, the interpretation given to any measured change in lung function, must be consistent with the standards established by the American Thoracic Society and European Respiratory Society (American Thoracic Society, 1994; American Thoracic Society, 2005). It is necessary to determine whether a measured change reflects a true change in pulmonary status or is only a result of technical or normal biological variation. Such variability is inherent in the spirometry test procedure, which relies completely on the willingness of the subject to expend maximal effort in test trials. The Society guidelines for interpretation are clear that even a 'statistically significant change may be of no clinical relevance' and that the 'largest errors occur when attempting to interpret serial changes in subjects without disease because test variability will usually far exceed any true decline' (American Thoracic Society, 2005).

As to the subjective reports of 'throat and ocular dryness', the criteria clearly state that 'the sensation of smell, unpleasant taste, tickling sensation and *dryness*…. are outside the scope of classification for respiratory irritation' (European Chemicals Agency, 2015). Thus, on the basis of the EU criteria reports of 'dryness' cannot be considered as indicative of respiratory irritation.

Three out of the four studies reviewed cannot inform on any association between exposure to propylene glycol and respiratory irritation, due to the mixed glycol exposures all cohorts experienced. As ECHA's CLP (2015) guidelines state, real-life human observational experience can be considered as long as 'exposure details are well documented and due consideration given to possible confounding factors', which is the case with the mixed exposures to multiple glycol compounds that are potentially greater irritants than propylene glycol. The key study conducted by Wieslander et al. (2001) that was relied upon did expose individuals to propylene glycol alone. However, the subjective symptom reports of throat and ocular dryness do not support the classification of respiratory irritation as these are not considered relevant sensations, according to the guidelines. The objective measurements, showing a small 5% pulmonary function decrease in only 4 out of 27 volunteers following exposure to propylene glycol, also do not indicate or constitute an adverse respiratory effect.

Therefore, the available scientific human data do not support the classification of propylene glycol as a respiratory irritant in humans.

1.2 The available animal data do not support the classification of propylene glycol as a respiratory irritant.

The proposed classification of propylene glycol as a respiratory irritant is reportedly supported by limited animal data on acute toxicity and indicative evidence from a repeated inhalation study. Analysis of these studies, however, indicates that there is insufficient scientific evidence presented that would support classification of propylene glycol as a respiratory irritant.

Four studies were cited as providing evidence for respiratory irritation:

Konrádová, V., Vávrová, V. and Janota J. (1978). Effects of the inhalation of a surface tension-reducing substance (propylene glycol) on the ultrastructure of the epithelium of the respiratory passages in rabbits. Folia Morphologica. 26:28-34

Robertson, O.H., Loosli, G.C., Puck, T.T., Wise, H., Lemon, H.M. and Lester W. (1947). Test for the chronic toxicity of propylene glycol on monkeys and rats by vapor inhalation and oral administration. J Pharmacol Exp Therap. 91:52-76.

Suber, R.L., Deskin, R., Nikiforov, I., Fouillet, X. and Coggins, C.R. (1989). Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats. Fd. Chem. Toxic. 27: 573-583

Werley, M.S., McDonald, P., Lilly, P., Kirpatrick, D., Wallery, J., Byron, P. and Venitz, J. (2011). Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. Toxicology. 287:76-90

The published papers by Robertson et al. (1947) and Konrádová et al. (1978) are not of sufficient quality, due to their limited experimental designs and methodologies; these limitations include: small numbers of animals/group, lack of adequate control animals, no rigorous statistical analysis, poor or no standardized and unbiased histopathological examination approaches that are mandated in current animal toxicology and safety assessments. Overall, the findings in these publications are incredulous and of no use for risk assessment and especially not for setting safety standards for propylene glycol.

The study design and methodologies of the published paper by Suber et al. (1989) also lacked the scientific rigor for assessing exposure-related toxicologic histopathology. For example, the authors provided no histopathological confirmation of the source or reason behind the “nasal bleeding” or “ocular discharge.” Red-tinged fluid around the nose and eyes due to excess porphyrin secretion sometimes is misdiagnosed as bleeding and is a common finding in rodents undergoing environmental stress (e.g., inhalation exposures). It is not clear if this was ruled out of the differential diagnosis. With a lack of histopathology in targeted tissues demonstrating hemorrhage it cannot be accurately concluded that propylene glycol exposure caused adverse effects (vascular rupture) responsible for the implied pathologies in hemostasis.

Interestingly, the authors of this subchronic nose-only inhalation study of propylene glycol, provided no details on the tissue sampling for light microscopic analysis of targeted organs in the respiratory tract (e.g., nose and lung) or descriptions of the histopathological sections (number and location) selected for examination. No unbiased quantitative pathology assessment (a common procedure in pathology today) of the only significant, but subjective, histopathology finding (increase in epithelial mucus) was conducted in this study. An unbiased quantitative assessment would have delineated and substantiated the severity and dose/response relationship for the increase of AB/PAS (Alcian blue and periodic acid-Schiff’s)-stained mucosubstances in the nasal epithelium. In addition, the study design lacked a post-exposure period (“recovery”) in filtered air which would have determined the persistent or transitory nature of this epithelial change.

<u>Most importantly, there is no description of any associated inflammatory cell response in the nasal mucosa.</u> <u>Exposure-related increases in the amounts of nasal epithelial mucus alone is not enough for an experienced respiratory pathologist to conclude that the propylene glycol exposure induced an adverse, rather than adaptive, effect on the nasal airway epithelium.</u> Without evidence of concurrent or preceding inflammation or epithelial cytotoxicity (cell death or degeneration) this single morphologic finding does not warrant a label of irritancy for propylene glycol at these levels of exposure. The increase in stored mucus in the nasal

airway epithelium can be a normal physiologic adaptive response that occurs with changes in humidity, temperature or other factors not related to chemical toxicity. This epithelial change is not uncommon in the nasal cavity of filtered air control animals and without a definitive etiology. Generally, chemical exposure-related inflammatory and/or other epithelial change (e.g., rhinitis, epithelial hyperplasia, hyalinosis) in association with mucous cell metaplasia/hyperplasia would warrant a definitive morphologic diagnosis of a pathologic response (adverse outcome) to the compound. However, no such finding was reported in this study after propylene glycol exposure.

It should also be noted that there is inconsistency in the light microscopic examination and histopathologic assessment in the more recently conducted inhalation studies of propylene glycol in rats and beagle dogs (Werley et al., 2011). Against the statement in the CLH report for propylene glycol that the Werley studies did not mention histopathological examinations, these can be found in chapters 3.3 and 3.4 of the publication. No single, statistically-supported, histopathologic finding (adverse effect) caused by inhaled propylene glycol was found in all of these reported studies. As noted in the CLH report for propylene glycol none of the acute, short-term inhalation exposure studies to propylene glycol included a full microscopic examination of the target tissues in the respiratory tract. Therefore, based on reported animal acute or repeated studies to date, there is no microscopic findings in the respiratory target organs of laboratory animals exposed by inhalation to propylene glycol aerosol that could be labeled as a histopathologic finding or morphologic adverse outcome in the targeted tissues.

According to the current definitions used by the CLH report, corrosive substances are those that destroy living tissues (cytotoxicity) and irritant substances are those non-corrosive substances that cause inflammation. There are no credible histopathology reports in the published literature that document -induced cytotoxicity or inflammation in the respiratory tract of propylene glycol inhalation exposed laboratory animals.

Therefore, the available scientific animal data do not support the classification of propylene glycol as a respiratory irritant in humans.

1.3 Propylene glycol's effects on the respiratory tract are likely indirect effects of the local drying of the airway mucosa due to the hygroscopic nature of this substance.

As discussed above, the available information does not demonstrate that propylene glycol meets the criteria for a respiratory irritant. Propylene glycol does not produce evidence of respiratory tract damage or irritant changes and rather the reported mild tissue changes and reported symptoms may be explained by simple drying effects on mucus membranes.

Propylene glycol is strongly hygroscopic and miscible with water under normal physiologic conditions (ATSDR, 1997). Many of propylene glycols uses take advantage of its physico-chemical hydroscopic properties so this property would similarly be anticipated to potentially dehydrate moist mucus membranes that may impart sensory symptoms and tissue adaptation responses. These same symptoms occur in low humidity climates to which adaptation

occurs. Thus the effects are not harmful or adverse and rather adaptive to the minor physiological change.

When deposited as a vapor or aerosol on the apical surface of the airway mucosa, propylene glycol will rapidly absorb water from the protective epithelial lining layer. The likely result of this is a rapid local increase in osmolarity. The drying effect of propylene glycol is analogous to breathing dry air which can result in decreased cell volume (Van Oostdam et al., 1986) and may result in epithelial changes (Chalon et al., 1972; Freed et al,, 1994; reviewed by Anderson and Holzer, 2002). Sensory nerve endings lining the conducting airways are sensitive to changes in osmolarity (Pisarri et al., 1992) and cell volume as evidenced by the cough that occurs in healthy human subjects inhaling nonisotonic aerosols (Eschenbacher et al., 1984; Higenbottam 1984). The drying effect of inhaled propylene glycol may be the underlying basis for the reported cough and feeling of airway irritation and a feeling of dyspnea reported in volunteers exposed to high concentrations (220 and 520 mg/m^3) of propylene glycol and/or other hydroscopic substance aerosol (Wieslander et al., 2001) and stage actors and show personnel exposed to glycols in theatrical fogs (Moline et al., 2000; NIOSH, 1992). In the NIOSH study, the fogs were generally composed of a mixture of glycols, with less than 2.1 mg/m^3 of propylene glycol and the reported concentrations were reported as TWA from personal and area monitors. While these exposures were associated with self-reporting of nasal symptoms (sneezing, runny or stuffy nose), respiratory symptoms (cough, wheeze, breathlessness, chest tightness), and mucous membrane symptoms (sore throat, hoarseness, dry throat, itchy, burning eyes) during their performances, no objective analytical measures were linked to these reports and the possibility of transient high exposure concentrations could not be ascertained from the reported TWA values.

An increase in osmolarity can also result in hypersecretion by mucous goblet cells of the surface epithelium and submucosal seromucous glands (Dwyer and Farley, 1997). The physical drying effect of inhaled propylene glycol aerosol is the likely mechanism leading to the observation of rapid hypersecretion of mucins from mucous goblet cells in the trachea of rabbits exposed for 20 or 120 minutes to 10% propylene glycol aerosols (Konradova et al, 1978). In this ultrastructural study propylene glycol exposure resulted in an increase in partially or fully discharged goblet cells. No recovery group was included in this study so the persistence of the morphologic alterations cannot be determined. The data from repeat exposure studies, however, suggest that exposure to high aerosol concentrations of propylene glycol do not induce epithelial injury or inflammation. Suber et al. (1989) exposed male and female Sprague Dawley rats to 0, 160, 1000, or 2200 mg/m^3 of propylene glycol aerosol 6 h/day, 5 days/week for 90 days. Rats exposed to the two highest concentrations of propylene glycol developed mucous cell hypertrophy/hyperplasia in the nasal respiratory epithelium as evidenced by an increase in the amount of stored AB/PAS stain sequence positive glycoproteins in mucous goblet cells. This is suggestive of an adaptive response to protect the epithelium from the repeated drying effects of high concentration propylene glycol aerosol exposure. There were reports of nasal hemorrhage and ocular discharge in a high proportion of the animals, however, there was no histopathologic evidence of nasal epithelial injury and there was no evidence of hemorrhage or ocular discharge on weekends when the animals were not exposed. This suggests that the

observations, if not just porphyrin staining, were likely due to increased nasolacrimal discharge resulting from the drying effects of the propylene glycol aerosol.

Therefore, the available evidence suggests that the reported findings in human and animal studies associated with exposure to high levels of propylene glycol aerosol are the result of the physicochemical properties of propylene glycol (e.g. hygroscopic and highly water soluble) and not the result of chemical toxicity. Furthermore, there is no evidence that propylene glycol is a sensory irritant. Suber et al. (1989) reported that male and female rats exposed to 160, 1000 or 2200 mg/m^3 of propylene glycol had no change in breathing frequency, minute volume or tidal volume. A decrease in breathing frequency in rodents is typical of a sensory irritant and serves to limit exposure to noxious xenobiotics by reducing the total inhaled dose.

Overall, the data demonstrate a lack of direct epithelial toxicity and rather suggest an adaptive response often associated with nontoxic irritant vapors and aerosols. The lack of reported airway epithelial injury or inflammation suggest that any perceived irritating effects of high concentration propylene glycol aerosols are indirect effects of the local drying of the airway mucosa due to the hygroscopic nature of propylene glycol. The ECHA CLP (2015) criteria clearly state that 'the sensation of smell, unpleasant taste, tickling sensation and *dryness*…. are outside the scope of classification for respiratory irritation' (European Chemicals Agency, 2015).

As some of the literature cited in the CLH report was published after the preparation of the lead dossier, a new literature research has been performed by the registrants and the information will be included in an update of the REACH Dossier.

2. The major producers of propylene glycol do not support propylene glycol's use as artificial smoke and electronic cigarettes.

The CLH report justifies the proposed classification evaluation based on the reported common use of propylene glycol to produce artificial smoke with generators in theatres, discotheques, emergency trainings or is used as a liquid for vaporisation in electronic cigarettes. Notably, this use is not supported by the major European producers of propylene glycol that have registered propylene glycol in the joint registration. In fact the major industry producers advise against this use on their public website (http://www.propylene-glycol.com/faq). Relative to the industry supported uses, the subject uses are incredibly small with estimates less than <0.1% of the propylene glycol used in Europe. The industry has taken notice on reported information and in the absence of sufficient information to support a scientific assessment for safe use, our present advice is against propylene glycol's use in this matter. Therefore rather than to propose classification based on the present insufficient information, it may be more appropriate to advise against these uses in the REACH dossier. Propylene glycol is a well-tested substance and demonstrated safe in supported industrial, consumer and medical applications however propylene glycol has not been properly tested to support intentional long term exposure to aerosol concentrations.

3. **Electronic cigarette issues are subject to a separate regulation (2014/40) and should not be a focus of the CLH report.**

Labelling as proposed in the CLH-report will be ineffective to protect consumers from possible harm by electronic cigarettes as labelling of tobacco products has to follow the provisions of EU Directive 2014/40 in Articles 10- 13. Instead, there are other instruments to tackle adverse effects from the use in tobacco or e-cigarettes:

According to Art. 20 of that Directive, manufacturers and importers of electronic cigarettes and refill containers shall submit a notification to the competent authorities of the Member States of any such products which they intend to place on the market. The notification shall be submitted in electronic form six months before the intended placing on the market. For electronic cigarettes and refill containers already placed on the market on 20 May 2016, the notification shall be submitted within six months of that date. A new notification shall be submitted for each substantial modification of the product.

The notification shall, depending on whether the product is an electronic cigarette or a refill container, contain the following information:

(a) the name and contact details of the manufacturer, a responsible legal or natural person within the Union, and, if applicable, the importer into the Union;
(b) a list of all ingredients contained in, and emissions resulting from the use of, the product, by brand name and type, including quantities thereof;
(c) toxicological data regarding the product's ingredients and emissions, including when heated, referring in particular to their effects on the health of consumers when inhaled and taking into account, inter alia, any addictive effect;

Furthermore, "In the case of electronic cigarettes and refill containers that comply with the requirements of this Article, where a competent authority ascertains or has reasonable grounds to believe that specific electronic cigarettes or refill containers, or a type of electronic cigarette or refill container, could present a serious risk to human health, it may take appropriate provisional measures. It shall immediately inform the Commission and the competent authorities of other Member States of the measures taken and shall communicate any supporting data. The Commission shall determine, as soon as possible after having received that information, whether the provisional measure is justified. The Commission shall inform the Member State concerned of its conclusions to enable the Member State to take appropriate follow-up measures."

Therefore the focus on electronic cigarettes within this CLH proposal is not necessary and will not increase consumers' safety.

4. **A new study is planned that will clarify propylene glycol's effects on the human respiratory tract. The major producers of propylene glycol are sponsoring a new human study to objectively assess the potential for propylene glycol aerosols to cause respiratory tract irritation.**

The major producers of propylene glycol are committed to understanding the health effects of propylene glycol. With the recent concerns raised about propylene glycol's potential to cause human respiratory irritation, the major producers have launched a new human study to be conducted at a leading research institute that well thoroughly examine acute exposures of propylene glycol aerosol to human respiratory tract and ocular responses. Presently the study has been contracted at the laboratory and is scheduled to begin with chamber testing for aerosol concentrations in May and then subject exposures starting in June. The study is expected to take 6 months to complete and hence results should be available before the end of this year to be reported thereafter. Given the importance of the proposed classification to propylene glycol and the significant new information this human study will contribute to the consideration for classification, ECHA and MS are respectfully requested to wait their conclusions on the proposed classification pending the availability of this study.

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