JTI's response to the BAuA proposal for a new CLP classification of Propane-1,2-diol

Currently propane-1,2-diol is not classified according to the Regulation (EC) No 1272/2008 (CLP Regulation) Annex VI. Recently, however, a new proposal for Harmonized Classification and Labelling was submitted to the European Chemicals Agency (ECHA) by the German Federal Institute for Occupational Safety and Health (BAuA). In their proposal, the BAuA suggested a harmonized classification of Specific Target Organ Toxicity –Single Exposure, STOT SE 3 (H335 may cause respiratory irritation).

JTI disagrees with the proposal of the BAuA to classify propane-1,2-diol as STOT SE 3 (respiratory tract irritant).

Human data

The proposal for STOT SE 3 (Respiratory Tract Irritation (RTI)) classification was primarily based on a publication by Wieslander *et al*., (2001), in which the authors investigated the effects of acute exposure to propane-1,2-diol mist on 27 non-asthmatic volunteers in a flight simulator. Wieslander *et al*., concluded that short exposures (1 minute) to propane-1,2-diol at 309 mg/m^3 (geometric mean) *"may cause acute ocular and upper airway irritation in non-asthmatic subjects. A few may also react with cough and slight airway obstruction*."

This study was conducted using a limited number of subjects, of which 8 had a history of atopy, hay fever or history of childhood eczema and more than half were either current or ex-smokers. According to the authors, 100% of those with atopy but only 28% of those without reported the development of throat symptoms (mainly dryness) and 4 subjects developed an irritative cough after exposure. Therefore, it is questionable if results from this study are representative for the general population. Additionally, no significant changes were detected in any measurements of nasal patency and lung function values remained essentially unchanged after exposure.

The authors also failed to provide any detailed information on the purity and composition of the propane-1,2-diol solution used. Substance purity information is key in establishing the hazard profile for a substance especially in the case of propane-1, 2-diol, as commercial solutions may also contain glycol derivatives (primarily ethylene glycol, triethylene glycol, 1,3-butylene glycol, dipropylene glycol, either as single ingredients or as a mixture).

The authors also reported the presence of formaldehyde as part of the exposure mist. However, in their discussion, the authors failed to address the potential effect of formaldehyde on any of the

observed symptoms and as such, their initial motivation for the determination of formaldehyde yields remains unclear. It should be noted that the reported concentration of formaldehyde in the test atmosphere was 58 times higher than the mean documented natural background concentration cited by the World Health Organization (2001). Additionally, short-term formaldehyde exposure to humans has been reported to result in eye, nose and throat irritation, followed by lachrymation, sneezing, coughing and dyspnea. Although the probability of the observed symptoms at the measured exposure concentrations is low, a synergic effect cannot be excluded. Furthermore, the authors documented the room temperature during exposure as 22.0-22.5°C with the mean air relative humidity in the flight simulator being 34%. According to Arundel *et al*., (1986) the majority of adverse health effects (including dryness of the nose and throat, and eye irritation) which may be caused by relative humidity would be minimized by maintaining indoor levels between 40 and 60%. In the light of this information the symptomatic events documented by Wieslander *et al*., (2001) may have been further confounded by the exposure conditions.

It should be noted that propane-1,2-diol is also used as a humectant in a variety of consumer products, drugs and medical devices where its function is to act as a carrier for active substances. Its hygroscopic properties are also well known and as such, the inhaled particles accumulate moisture as they traverse the upper respiratory airways. This may cause occasional throat dryness, a symptom reported by Wieslander *et al*., (2001). However, according to the CLP guidance on the classification criteria for respiratory tract irritation (Annex 1: 3.8.2.2.1) it is stated that:

"Symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" shall be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, <u>and dryness, which are outside the scope of classification for respiratory irritation</u>".

As such, 'dryness' would be outside the scope for the proposed STOT SE classification.

Additionally, according to *the CLP regulation "respiratory irritant effects are characterized by localized redness, oedema, pruritis and/or pain that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included (…). Subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids)".*

Wieslander *et al*., (2001) did not report any evidence of respiratory tract redness, oedema, and inflammation or breathing difficulties. Additionally, the study is of limited value in the absence of an air control group.

The BAuA also used results from Wieslander & Norbäck (2010) to support their classification. This study evaluated general symptomology, as well as ocular and nasal biomarkers in house painters as a way to estimate their personal exposure to volatile organic compounds (VOC) and microbial VOC (MVOC) during indoor painting with water-based paints (WBP). These subjects

were exposed to propane-1,2-diol as a mixture with other glycolic compounds (mainly diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, and 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate) and to several MVOCs, and as such any documented irritative effects to the eyes and nasal mucosa could not be attributed to propane-1,2-diol alone. This conclusion would also hold true for the studies conducted by the National Institute for Occupational Safety and Health (NIOSH) (cited in NTP report (2004)) and Moline *et al*., (2000) where documented symptoms following exposure to theatrical fog (a mixture of several glycols) cannot be used as representative information for propane-1,2-diol exposure.

Animal data

For supporting animal studies, the BAuA cited several acute and short-term studies in rabbits, rats and Beagle dogs (Konradova *et al*., 1978; Suber *et al*., 1989; Wang *et al*., 2007, Werley *et al*., 2011).

Konradova *et al*., (1978) used a limited number of animals (3 rabbits), exposed to 10% propane-1,2-diol for 20 minutes and 3 rabbits exposed for 2 hours. Results indicated that a twenty-minute exposure period induced minimal ultrastructural changes of the trachea with signs of pathological alterations only being observed for the 2-hour exposure period (no other observations were reported).

Suber *et al*., (1989) reported the results from a 13-week nose-only inhalation exposure to propane-1,2-diol in rats. Results failed to show significant changes in respiratory rates, tidal volumes or minute volumes in comparison to the control group. Any documented increase in the number of goblet cells or increase in mucin content of the goblet cells were reportedly due to the hygroscopic properties of propane-1,2-diol and not due to RTI or cytotoxic effects. Additionally, this study is a repeated exposure study and there is no information if the same effect would be observed after single exposure as suggested by the submitter.

The BAuA also commented on an acute inhalation toxicity study conducted by Werley *et al*., (2011) in which they interpret a transient decrease in body weight as *"the single 4 h inhalation must have affected the general health condition of the exposed animals, although no specific clinical observations were reported during and directly after the exposure*". These observations are consistent with other published data indicating that weight loss is not correlated with exposure but is rather due to the stress produced by the treatment restraint (Harris *et al*., 1998; Rybkin *et al*., 1997). In the same publication, the rats' exposure to high concentrations of propane-1,2-diol for 28 days produced only "minimal" laryngeal squamous metaplasia. This was explained by authors as *"a lesion commonly observed in many different inhalation exposure studies and probably related to the unique sensitivity of the larynx, and its capacity for efficient deposition of particles."* No histopathological changes were reported for the nose and throat, which are the

primary exposed organs in such a study after single or repeated exposure. Additionally, in the 28-day study in dogs, no histopathological effects on the laryngeal, tracheal and lung tissues were observed.

Conclusion

The studies proposed by the dossier submitter are not supportive of the propane-1,2-diol classification as STOT SE 3.

BAuA predominantly based their proposal on a single study that has been conducted with an undefined propane-1,2-diol solution, on a limited number of human subjects deemed to be predisposed to allergy.

Other human studies presented in the BAuA's dossier do not describe specific respiratory irritant effects due to exposure to propane-1,2-diol only but rather to glycol mixtures.

Propane-1,2-diol has hygroscopic properties and when placed in an atmosphere containing water vapor, it will collect and retain moisture, which may provoke in some instances dryness leading to mild cough, which are transient and reversible effects. Dryness is outside the scope for classification of substances as respiratory tract irritants.

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