COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: propane-1,2-diol
CAS number: 57-55-6
EC number: 200-338-0
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Belgium		Individual	1
Comment received				
http://www.ncbi.nlm.nih.gov/pubmed/18158714 http://www.ncbi.nlm.nih.gov/pubmed/12636164 http://www.ncbi.nlm.nih.gov/pubmed/21476863 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4088352/				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Germany		Individual	2
Comment received				
Who ever wrote this enquiry is ignoring scientific facts and will never bevable to provide proof. If it was [redacted] from the [redacted]: ignore her! This will save you a lot of money and time. REFERENCES: Preclinical safety evaluation of inhaled cyclosporine in propylene glycol http://www.ncbi.nlm.nih.gov/pubmed/18158714 Lung deposition and pharmacokinetics of cyclosporine after aerosolization in lung transplant patients. http://www.ncbi.nlm.nih.gov/pubmed/12636164 Safety and toxicology of cyclosporine in propylene glycol after 9-month aerosol exposure to beagle dogs http://www.ncbi.nlm.nih.gov/pubmed/21476863				

Lung Deposition and Pharmacokinetics of Nebulized Cyclosporine in Lung Transplant Patients - 2014 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4088352/
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Sweden		Individual	3
Comment received				
Propylene glycol has a fairly long history of non-problematic use. Uses include being constituent of pharmaceutical preparations of many types. Implying that it is toxic through single exposure is just outright silly.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	4
Comment received				
My concerns with this research are not specifically with the research, but with the massive missed opportunities on the research, the conclusions reached and the potential knock on effects on a wider scale The research appears to show minimal harm in animal testing, and does not justify the classification of PG as a harmful substance - a substance that is used in asthma inhalers, electric cigarettes, and in an amusingly contrary example which rather questions the supporting research, is used to carry anti-rejection drugs more effectively in lungs after human transplantation: http://www.ncbi.nlm.nih.gov/pubmed/12636164 It should also be noted that the timing of this research smells fishy at best when considering that (with what can only be described as specious at best, and mendacious at worst) attempts at slighting electric cigarettes in the public health world continue, despite the fact that they are - by a wide margin - the safest way to successfully substitute smoking lit tobacco, which is well known to kill not only 1 in 2 of lifelong users, but also cause three house fires a day, and one in two accidental deaths caused by fire in London *alone*: http://www.london-fire.gov.uk/Smoking.asp While I would not go as far as to cry 'conspiracy' - primarily because I'm not a gibbering moron - it's clear to see that this research could be used politically to attempt to unjustifiably restrict the usage of electric cigarettes (as recently seen in Wales - http://www.theguardian.com/society/2015/dec/08/welsh-government-amends-plans-for-e-cigarette-ban-vaping - which used exactly this sort of circumstantial 'research' as evidence to attempt to prevent the use of e-cigs in public places, despite the quoted reseach not being remotely relevant to the use of such devices). Regulation that was only				

stopped with large amounts of campaigning, and in the end, by nothing more than just plain bad luck (an assembly member speaking out of turn, amusingly/tragically/atrociously enough).

A far better source of information on the effects of PG on the respiratory tract would have been to actually talk to people who regularly use it, and perhaps, study them.

Users of electronic cigarettes are the ideal candidates for investigating suggestions of harm from PG, but as with almost all regulation that affects them directly, at no stage were users of electronic cigarettes consulted - even though they are referred to in the study.

My concern is not that someone thought that it was worth studying the irritability of PG; that is laudable and a point I will return to shortly. However, the manner in which this study was instigated, the methodology used and it's applications to the real workd, the timing of the study and how the (non-human) result has assessed potential danger utterly ignores the fact that there are several *million* actual human beings in the EU inhaling not insignificant doses of PG, all day, every day:
http://www.tobaccoatlas.org/topic/e-cigarettes/
See 'prevelance and use - these numbers have increased significantly since 2012, with over two million in the UK alone:

http://www.ash.org.uk/media-room/press-releases/:over-2-million-britons-now-regularly-use-electronic-cigarettes

The users of these devices would have made for a far more useful basis for report of harm in humans, and frankly, we'd be glad of the opportunity to actually have a hand in some proper research, rather than the users being ignored yet again, and unconnected research being performed and undoubtedly used as evidence to legislate against us - as unconnected research like this often has in the past by certain members of the (highly funded by tobacco use) tobacco control circuit.

This is especially true as there *are* a limited number of people who report being sensitive to liquids that contain >50% PG (it can cause a dry throat/mouth); it would be very interesting to see trials on this subject as it would help inform consumers on which liquids they might benefit from avoiding when attempting to stop smoking - as the vast majority of users are smokers or ex smokers, a habit of which the resulting diseases are recognised as being the primary health issue of our times, directly affecting almost everyone in Europe either via second hand smoke, fire hazard or the fact that almost everybody knows someone who has died of a lit tobacco related disease.

Long story short - I personally do not believe that the levels of irritation shown in the studies attached warrant the classification of PG as a hazardous substance. Also, that the 'knock on' effects of this classification need to be considered on an ethics and public health standpoint, as I will happily guarantee that the 'usual suspects' - Australia, Canada, and various 'personalities' within the realm of junk science peddlers - will gladly misuse this research to push an anti-science, anti-public health agenda based on their apparent hatred of attempting to stop smoking using methods that are not sanctioned by public health bodies.

And I appreciate that my comment may be somewhat rambling (and I swear, I'm not a conspiracy theorist nutbag, just a concerned citizen), but I would hope that whomever this may come in front can appreciate why I have concerns and ideally understand why my concerns should not be idly set aside.

The press and various 'interesting' characters in public health (the sort who have to specifically preface their medical advice as not being medical advice - Dr Oz, Gillian McKeith etc) love a good scare story, and it is in your interests from an ethical standpoint to not enable this with statements on the hazards of substances that are not terribly well supported by the research, contradicted in widespread real world usage and open to interpretation or abuse.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	France	GAIATREND	Company-Manufacturer	5

Comment received

Commentaires suite à la proposition pour le CLP de modification de la classification de la substance propane-1,2-diol (numéro cas 57-55-6) en STOT SE 3

Après lecture de ce document, nous constatons que ce dossier **bibliographique** pose un certain nombre de remarques.

En effet, ce document est établi à charge à partir de **quelques commentaires issus du web et non contrôlés**. En effet, il s'avère que les intolérances révélées sont bien souvent liées à certaines substances, notamment aromatiques.

Nous observons également qu'il existe seulement **deux publications du même auteur sur l'interaction homme / propane-1,2-diol**. Elles consistent à placer des personnes dans une pièce, maintenue dans un brouillard durant 1 minute. Force de ce constat, Gaïatrend a d'ailleurs lancé un projet ambitieux avec des partenaires indépendants afin de caractériser et modéliser les interactions entre le corps humain et les vapeurs issues de ses e-liquides. Cette étude portera sur une population de 100 personnes.

Les **conditions opératoires** de ces essais sont différentes et assez peu réalistes. En effet, il est peu commun de se retrouver dans une pièce étanche sans évacuation saturée par un brouillard de propane-1,2-diol durant près de 1 minute avec une concentration de 800 mg/m3 de propane-1,2-diol.

Les publications sur les **animaux** sont assez peu pertinentes car le système cardiovasculaire est assez éloigné de celui de l'être humain. L'animal le plus proche de l'homme d'un point de vue cardiovasculaire étant le cochon.

A la page 19, nous observons que les données physiologiques du poumon avant et après exposition à la substance propane-1,2-diol sont identiques. La différence de FEV1 avant et après exposition n'est pas **significative** et n'est pas documentée (différence 1%, 103% contre 102%, incertitudes). Ce pourcentage peut être par ailleurs expliquée par le fait que la molécule gazeuse de propane-1,2-diol n'a pas la même caractéristique que l'air en terme de viscosité.

D'autre part, il apparait également que la **qualité** du propane-1,2-diol n'est pas précisée. Il s'avère que cette qualité est très importante car cette molécule est généralement

accompagnée d'autres molécules organiques indésirables et cela même pour du propane-1,2-diol répondant aux exigences de qualité EP ou USP. En effet, selon son origine et les procédés de synthèse nous retrouvons :
*le mono et le di éthylène glycol qui sont nocifs à 0,1%,
*le di propylène glycol qui est également nocif à 0,1%,
*l'oxyde d'éthylène qui est cancérigène pour des concentrations comprises entre 10 et 80 ppm.

Ces molécules nocives ne sont pas suffisamment traquées par la réglementation EP ou USP car leurs concentrations sont en dessous des seuils admis de quantification. Dans bien des cas, l'irritation est liée à la présence de ces molécules organiques, notamment dans le propylène glycol d'origine **végétale.**

La conclusion est que peu d'études sur l'inhalation du propane-1,2-diol par l'être humain ont été réalisées. Les protocoles doivent être rigoureux et réalistes, tout en maîtrisant la qualité de la substance utilisée. Nous considérons que lorsqu'il y a un doute sur une molécule, le meilleur moyen de le lever est de le démontrer par l'expérience. La bibliographie est une aide précieuse pour mettre au point ces études pertinentes et indépendantes.

A ce titre, Gaïatrend vient de lancer un projet ambitieux avec des partenaires indépendants afin de caractériser et modéliser les interactions entre le corps humain et les vapeurs issues du propane-1,2-diol seul, et aromatisé. Cette étude portera sur une population de 100 personnes durant 18 mois.

ECHA note - The following attachment was submitted with the comment above: *Commentaires suite à la proposition pour le CLP de modification de classification de la substance PG.docx*

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2016	United Kingdom		Individual	6

Comment received

This classification proposal is the weakest and most poorly justified I have seen in 20 years of working in this area. Junk science websites are used as sources of information to justify the investigation plus a very, very small number of submissions to the C&L inventory (just 3 out of nearly 5000 have submitted a correctly completed notification indicating a classification for respiratory irritation). The subsequent 'hard' scientific evidence offered to justify the proposal is limited and weak at best and the responses reported, which using the proposal author's own description were mild, do not meet the criteria for classification for respiratory irritation. Whilst the author claims to be using a weight of evidence approach, no negative studies are included in the proposal.
The proposal is entirely based around the specific use of the substance monopropylene glycol (MPG, propane-1,2,diol) in aerosol form when used in two very specific and minor applications (in tonnage terms) – use as a carrier in e-cigarettes and use to generate theatrical fogs. No evidence is offered that any adverse effects result from vapour exposure. The EU has a 'Better regulation' initiative that is about designing EU policies

and laws so that they achieve their objectives at minimum cost and making EU laws more effective and efficient. (http://ec.europa.eu/smart-regulation/index_en.htm). This classification proposal does not meet these criteria. Classification of MPG as a respiratory irritant will not be effective since e-cigarettes would be outside of scope of the CLP regulation and it would not necessarily prevent continued use in artificial fogs (as a simple assessment would show no risk.) However, it would impose significant costs on the vast majority other users where no hazard is present. A far more effective legislative instrument both in terms of minimising economic costs and potential desired impact would be a proposal for a restriction on these two identified uses through the submission of an Annex XV restriction proposal under REACH. This would be a far more targeted approach that would allow a proper consideration of the hazard data against the socioeconomic benefits and the hazards of likely alternatives than the current inappropriate CLP approach. I would therefore urge the Commission and ECHA to encourage the German competent authority to withdraw this proposal and, if following the comments received from this consultation there still remains residual concern over these two uses, ask them to replace it with an Annex XV restriction proposal for in scope uses rather than waste the precious time of the Risk Assessment Committee on a CLP discussion.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	Switzerland		Individual	7
Comment received				
Billions of users of electronic cigarettes are inhaling Propylene glycol daily, for many years, without experimenting any issue. This experience should be taken into account. It shows Propylene glycol is not dangerous for the respiratory system.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United States		Individual	8
Comment received				
I apologize I have no scientific info to add to my opinion, but I feel that this is just another method being used to make vaping look bad despite how much better anyone can clearly see is better than smoking a burning cigarette.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number

22.04.2016	France	FIVAPE / Fédération Interprofessionnelle de la Vape	Industry or trade association	9
Comment received				
Selon notre fédération les critères ne sont absolument pas suffisant pour envisager un classement du Propane-1,2-diol en catégorie STOT SE 3. Nous sommes absolument surpris par la démesure du classement proposé au regard du nombre d'études existantes et de l'ancienneté des connaissances du le sujet. Ceci est à mettre en regard avec la pauvreté de l'argumentation du rapport CHL qui se base sur des échantillons ridicules au regard des 20 millions de vapoteurs qui inhalent quotidiennement du MPG sans aucun des effets cités. Nos commentaires se trouvent dans le fichier attaché. ECHA note - The following attachment was submitted with the comment above: *PG_STOTSE3_com_FIVAPE*				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany	Günther Schaidt SAFEX-CHEMIE GMBH	Company-Downstream user	10
Comment received				
The worldwide consumption of fog fluid is reckoned annually about 158 million liters. The consumption of fog fluids since the first presentation on the market (in 1973) until 2015 = 42 years will be also estimated about 4.7 billion liters "worldwide". The figures are conservatively estimated values for Europe and USA. Values for Africa, Asia, Australia and South America are not included in the figures, as a serious, even rough estimate was not possible, due to lack of basic data. (See page 2 of the Safex-rejection request) The internet discussions outlined in the BauA-proposal on the subject of Theatre Fog do not justify any urgent action, partly, because since the appearance of the Wieslander Cockpit publication 17 years ago no symptoms that were com-plained of have been described in international databases or specialist publications (technical literature/ professional journals) and, secondly, the WWW discussions as listed are completely on an unscientific, amateur level. (See page 2 of the Safex-rejection request) Attached is a review of Cpt. Dipl.-Ing. Thomas Krieg, Hamburg, Sea-Med-Care, Basic Safety Training Instructor, presenting the impressive evidence that in emergency trainings, carried out since 1985, comparable to those described in the Wieslander study with a total of about 54,000 people, no irritations / adverse effects have occurred as described in the BauA-proposal. Occasionally emerged problematic situations could be attributed to psychosomatic causes and not to substance-based effects of PG. (See „T. Krieg Erfahrungsbericht Anwend. v. Theaternebel bei Notfalltrainings 2015.pdf“) As evidence for adverse effects of PG as a constituent of Theatre fog only one study was presented with human data that has never been repeated. This study is in terms of its design, implementation and documentation on such a low level that it does not nearly meet scientific standards, particularly with regard to comprehensibility. (See "Studienkritik Wieslander K. Ultes.pdf")				

Because of coarse documentation lacks, it remains unclear whether PG was used in the study as the sole substance for fog generation. The composition therein designated as "commercial PG solution" is not specified at any point; it remains completely unclear in what or with what the PG was dissolved. As evidenced by the term of "solution", it is therefore undoubtedly a PG-containing liquid with other, unknown ingredients. (See page 4 of the Safex-rejection request)

The study design and execution of experiments with volunteers in the cockpit study was so flawed that other causes such as exam stress, fear of the fog , odor and sensory nuisance, air dryness, previous medical awkward interviews and tests (squint-test), cockpit claustrophobia , iatrogenic prejudice etc. in the sense of psychosomatic defense reactions are most likely. The parameters and the circumstances of the tests cannot be verified due to the extremely poor documentation. Even in terms of quality, the type and condition of the fog machine used, no statements are made. (See page 5 of the Safex-rejection request)

Because of this lack of documentation violating scientific principles, the study is already inadequate to evaluate evi-dence for the claimed effect of PG.

Virtually all studies cited as supportive evidence in the BauA-proposal exhibit some grotesque contradictions opinion of the applicant, that are not considered by him and not well explained either. In particular the study with 105 children, described on page 6 of the attached Safex-rejection request.
An other example is the extensive reference to several US-musical-singer studies represent in the scientific sense a confirmation bias and an illusory correlation error due to the perception of a causal relationship between two events. (See page 12 of the Safex-rejection request)

The studies report about 6 to 8 musicals with fog application and 5 musicals where no fog of any kind was used. The reports make unequivocally clear that the expressed symptoms the soloists complained of were attributed by them to the fog exposure which also occurred in completely the same way in the musicals that had been carried out without fog. Obviously, physical burden, at least with US Music soloists are so massive that they suffer significantly from respiratory irritation of various kinds, which is known to every expert on the basis of strong vocal and physical extreme strain by dancing and singing, in particular due to the high competition in USA. (See page 12 of the Safex-rejection request)

The SAFEX® request for rejection of the BauA-proposal is supported by accompanying documents, in particular by current experience reports of a variety of fog fluid users in German-speaking countries (theater and entertainment industry). (See „Aktuelle Erfahrungsberichte deutscher Nebelanwender 2016.pdf")

For the above reasons and the accompanying detailed SAFEX® rejection request it is required to reject the BauA –proposal to ECHA for future marking of Propane-1,2-diol as respiratory irritation = STOT SE 3, H335.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Belgium	The Electronic Cigarette Industry Platform on REACH ("eCIP")	Industry or trade association	11

Comment received

The Electronic Cigarette Industry Platform on REACH ("eCIP") is the International Association representing companies operating in the EU and involved in the distribution of electronic cigarettes and/or refill containers. The vision of eCIP is to address matters concerning the e-cigarette and e-liquids industry as affected by chemical management regulations such as REACH and the CLP.

Members of the Electronic Cigarette Industry Platform (eCIP) oppose the dossier submitter's proposal to classify propane-1,2-diol as STOT SE 3; H335.
Propane-1,2-diol does not meet the criteria for classification for any of the physical, health or environmental hazards laid down in Parts 2 to 5 of Annex I of the CLP and therefore, it should not be classified.
Further, as a justification for why action is needed at community level in page 9 of the CLH report, the dossier submitter states that "several notifiers used STOT SE 3 in the self-classification, whereas the majority of notifiers proposed no self-classification at all."
This statement must be placed in the correct perspective where data available on the ECHA dissemination webpage demonstrates that only a minor percentage (0.16%) of notifiers have reported STOT SE 3;H335 for propane-1,2-diol (C&L inventory: 4966 notifiers proposed no-self classification and only 8 notifiers used STOT SE 3; H335).
Propane-1,2-diol is a registered substance under REACH for a high tonnage band (tonnage band 100 000 – 1 000 000 tonnes per annum). The 68 registrants support that propane-1,2-diol should not be classified, also based on a sub-chronic nose inhalation study in Sprague-Dawley rats (Suber et al., 1989).
The REACH dossier of propane-1,2-diol was not even considered in the dossier submitter's proposal. Instead, the dossier submitter's used primarily a single study on human volunteers (Wieslander et al., 2001) as well as data on human experience obtained from internet fora communications as part of its scientific justification for the proposal (page 8).
Also, the CLH report provides under section 4.3.2 Comparison with criteria (page 27) that "no fully reliable animal study on acute irritation effects on the respiratory tract is available".
First, this statement is self-contradicting as the same CLH report cites Werley's, Suber's and Konradova's studies as supportive evidence of the irritative nature of propane-1,2-diol on the same page (page 27).
Second, contrary to the dossier submitter, the EMA report (CHMP, 2013) judged the experimental studies of Werley and Suber, which confirmed no adverse effects on the animals, to be reliable.
Specific comments on the relevance and adequacy of the set of data used by the dossier submitter for the purpose of classifying propane-1,2-diol are discussed in the specific comments section below.

ECHA note - The following attachment was submitted with the comment above: *Annex I to eCIP comments HCL proposal PG final 21042016*

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	United Kingdom	Independent British Vape Trade Association	Industry or trade association	12
Comment received				
The Independent British Vape Trade Association (IBVTA) welcomes the opportunity to respond to this consultation. IBVTA is a not-for-profit trade association representing all responsible and ethical independent vaping businesses in the UK irrespective of the size of their companies and operations. All IBVTA members are free from any ownership or control by the tobacco and pharmaceutical industries. Propylene glycol (propane-1,2-diol, PG) is a substance widely used throughout different industries. It appears the dossier submitter has based his assessment of a need for classification on unreliable internet data from chats and forums with no scientific evidence. Moreover, the choice of scientific studies by the submitter is flawed and as a result, the CLH report is not scientifically robust enough to consider the introduction of Propylene glycol in Annex VI of CLP.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2016	Belgium		Individual	13
Comment received				
Propylene Glycol has been, and still is, one of the main ingredients of well-known and approved medicinal inhalers. Furthermore it is also widely used as a suspension agent for watersoluable flavorings, an antibacterial agent for beautyproducts such as soap, showergels, shampoos, conditioners, moisturizing creams, et cetera.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	France		MemberState	14
Comment received				
We agree with the classification proposal STOT SE 3, H335				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Belgium	UBV-BDB	National NGO	15

Comment received
Le Propylène Glycol en médecine : Le propylène glycol (C3H802) est un médicament solubilisant communément utilisé pour les médecines topiques, orales et injectables. Il est utilisé comme stabilisateur pour des vitamines et comme cosolvant miscible dans l'eau. Le propylène glycol est utilisé comme solvant pour la cyclosporine dans une préparation pharmaceutique utilisée pour le traitement de patients suite à une transplantation pulmonaire (voir les références en bas de page). Je me demande pourquoi cette information (assurément scientifique) n'est pas citée dans la proposition. Au fait - les spray à la nicotine (Nicorette, QuickMist) utilisent aussi du propylène glycol comme solvant pour la nicotine.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany		Individual	16
Comment received				
Der vorliegende Antrag ist aus meiner Sicht zum jetzigen Zeitpunkt zumindest im Kontext Theaternebel nicht nachvollziehbar. Durch die vorliegenden Belege ist nach unserer Einschätzung nicht transparent begründet, dass eine Reizung der Atemwege in einem kausalen Zusammenhang mit Propane-1,2-DIOL steht. Insofern ist allein aufgrund der angeführten Belege eine Kennzeichnungspflichtig mit dem Piktogramm GHS07 nicht zu rechtfertigen. Insofern kann der Antrag unseres Erachtens aufgrund fehlender Nachweise nur abgelehnt werden. Eine wissenschaftlich fundierte Studie zur tatsächlichen Einordnung der Gefährdungen durch Propane-1,2-DIOL, insbesondere durch Inhalation von Bühnennebel, würde ich begrüßen. Rainer Münz ehemaliger Technischer Direktor Mir sind in diesem Zusammenhang bisher keine gesundheitlichen Beeinträchtigungen bekannt geworden.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany		Individual	17
Comment received				
Die GESTIS-Datenbank des IFA Institut der Deutschen Gesetzlichen Unfallversicherung stuft den Stoff als unkritisch und nicht kennzeichnungspflichtig ein. Eine Kennzeichnungspflicht erschwert den Einsatz von Show-Nebel unverhältnismäßig schwer.				

Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany		Individual	18

Comment received

The present evaluation is not acceptable from my perspective at the present time, at least in relation to theatre fog. In our estimation, this evidence offers no transparent justified proof that a respiratory irritation is causally associated with Propane-1,2-DIOL. In this respect, a compulsory labelling with a pictogram GHS07 cannot be postulated solely on the basis of the listed documents.

We are aware that many remarks from internet forums and some media reports are not relevant comments. The Commission will recognize this and they certainly require no further commentary. The studies however, are partially deficient in design and execution and provide no reliable information on actual threats due to inhalation exposure.

To that extent, the application must, in our opinion, due to the absence of evidence, be rejected.
We would welcome a scientifically sound study to actually classify and determine possible hazards of the use of Propane-1,2-DIOL, especially through the inhalation of theatre fog. At the present time, we know of no health injuries in regard the the use in the theatre on in live entertainment.

Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany		Individual	19

Comment received

The present evaluation is not acceptable from the perspective of VPLT at the present time, at least in relation to theatre fog. In our estimation, this evidence offers no transparent justified proof that a respiratory irritation is causally associated with Propane-1,2-DIOL. In this respect, a compulsory labelling with a pictogram GHS07 cannot be postulated solely on the basis of the listed documents.

We are aware that many remarks from internet forums and some media reports are not relevant comments. The Commission will recognize this and they certainly require no further commentary. The studies however, are partially deficient in design and execution and provide no reliable information on actual threats due to inhalation exposure.

To that extent, the application must, in our opinion, due to the absence of evidence, be rejected.
We would welcome a scientifically sound study to actually classify and determine possible hazards of the use of Propane-1,2-DIOL, especially through the inhalation of theatre fog.

At the present time, we know of no health injuries in regard the the use in the theatre on in live entertainment.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany		Individual	20
Comment received				
The present evaluation is not acceptable from the perspective of me opinion at the present time, at least in relation to theatre fog. In our estimation, this evidence offers no transparent justified proof that a respiratory irritation is causally associated with Propane-1,2-DIOL. In this respect, a compulsory labelling with a pictogram GHS07 cannot be postulated solely on the basis of the listed documents. We are aware that many remarks from internet forums and some media reports are not relevant comments. The Commission will recognize this and they certainly require no further commentary. The studies however, are partially deficient in design and execution and provide no reliable information on actual threats due to inhalation exposure. To that extent, the application must, in our opinion, due to the absence of evidence, be rejected. We would welcome a scientifically found study to actually classify and determine possible hazards of the use of Propane-1,2-DIOL, especially through the inhalation of theatre fog. At the present time, we know of no health injuries in regard the the use in the theatre on in live entertainment.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany	Unfallkasse NRW	National NGO	21
Comment received				
Sehr geehrte Damen und Herren, zur beabsichtigte Forderung eine Kennzeichnung des Stoffes Propane-1,2-Diol kann ich Ihnen folgendes mitteilen: Der v.g. Stoff ist in der GESTIS- Stoffdatenbank des Institutes für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA) offensichtlich nicht kennzeichnungspflichtig. Zusammenfassend wird in dem Abschnitt zur Akuten Toxizität folgendes ausgesagt: „Zusammenfassend wird von einem allenfalls schwachen hautsensibilisierenden Potential ausgegangen, das keine Kennzeichnung erfordert." Siehe: http://gestis.itrust.de/nxt/gateway.dll?f=templates$fn=default.htm$3.0				

Der vorliegende Antrag ist zum jetzigen Zeitpunkt im Kontext Theaternebel nicht nachvollziehbar. Durch die vorliegenden Belege ist nicht transparent begründet, dass eine Reizung der Atemwege in einem kausalen Zusammenhang mit Propane-1,2-DIOL steht. Insofern ist allein aufgrund der angeführten Belege eine Kennzeichnungspflichtig mit dem Piktogramm GHS07 nicht zu rechtfertigen.

Insofern ist der Antrag aufgrund fehlender Nachweise abzulehnen.
Eine wissenschaftlich fundierte Studie zur tatsächlichen Einordnung der Gefährdungen durch Propane-1,2-DIOL, insbesondere durch Inhalation von Bühnennebel, ist zu begrüßen.

Mit freundlichen Grüßen

Mit freundlichen Grüßen

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Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany		Individual	22
Comment received				
The present evaluation is not acceptable from my perspective at the present time, at least in relation to theatre fog. In my estimation, this evidence offers no transparent justified proof that a respiratory irritation is causally associated with Propane-1,2-DIOL. In this respect, a compulsory labelling with a pictogram GHS07 cannot be postulated solely on the basis of the listed documents. I am aware that many remarks from internet forums and some media reports are not				

relevant comments. The Commission will recognize this and they certainly require no further commentary. The studies however, are partially deficient in design and execution and provide no reliable information on actual threats due to inhalation exposure.

To that extent, the application must, in my opinion, due to the absence of evidence, be rejected.
I would welcome a scientifically sound study to actually classify and determine possible hazards of the use of Propane-1,2-DIOL, especially through the inhalation of theatre fog. At the present time, I know of no health injuries in regard the use in the theatre on in live entertainment.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Netherlands	Fontem Ventures	Company-Manufacturer	23

Comment received

The German Federal Institute for Occupational Safety and Health (BAuA) submitted to the European Chemical Agency ("ECHA") a proposal for Harmonized Classification and Labelling (CLH dossier dated October 2015) of Propylene Glycol as STOT SE 3, with the hazard phrase H335: May cause respiratory irritation.

According to Fontem's analysis, the data purporting to justify the STOT SE 3 H335 classification proposal do not provide sufficient evidence to warrant CLP classification with respect to respiratory irritation.

Please see the attached paper for our more detailed analysis.

ECHA note - The following attachment was submitted with the comment above: *Fontem Ventures - Comments on CLP Report - Proposal for Harmonised Classification and Labelling*

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	24

Comment received

Are you all completely mad ? With all the scientific evidence starting from the 1940's showing the complete oppisite to PG being toxic, it's used throughout the medical and food industries showing only beneficial results, you want to class it as toxic ? With no scientific evidence to support such a classification, all you can hope to achieve by such a course of action will be to lead to more deaths from smoking, as it would appear that your organisation and a few others are doing the best you can to keep people smoking to get as much money as possible out of people before they die, well I hope you've got good

lawyers, because I can see a time when vaping is shown without a doubt (as the evidence is pretty much there now) that it saves lives, and the lawyers will be going after everyone who deliberately stood in the way of saving lives, as the lawyers are doing to the tobacco industry after they kept claiming that smoking didn't kill people !!
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United States		Individual	25
Comment received				
I have used propylene glycol (PG) in my eliquid since November 7, 2012 and have been a moderate to heavy user of this substance. In that time I have never had a problem with its usage.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Germany	VPLT - Verband der Medien- und Veranstaltungstechnik	Industry or trade association	26
Comment received				
The present evaluation is not acceptable from the perspective of VPLT at the present time, at least in relation to theatre fog. In our estimation, this evidence offers no transparent justified proof that a respiratory irritation is causally associated with Propane-1,2-DIOL. In this respect, a compulsory labelling with a pictogram GHS07 cannot be postulated solely on the basis of the listed documents. We are aware that many remarks from internet forums and some media reports are not relevant comments. The Commission will recognize this and they certainly require no further commentary. The studies however, are partially deficient in design and execution and provide no reliable information on actual threats due to inhalation exposure. To that extent, the application must, in our opinion, due to the absence of evidence, be rejected. We would welcome a scientifically sound study to actually classify and determine possible hazards of the use of Propane-1,2-DIOL, especially through the inhalation of theatre fog. At the present time, we know of no health injuries in regard the the use in the theatre on in live entertainment.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	Germany		Individual	27
Comment received				
It has been considered safe for decades in various uses. Theater Fog for instance.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	28
Comment received				
Electronic cigarette liquids almost always contain Propylene Glycol (PG) and have been in very widespread use across the EU and Worldwide for many years without any evidence of acute or chronic toxicity at these or any doses. In fact, given that the delivery of PG in vapour form is so directly targeted at the respiratory tract it would seem reasonable that extraordinary evidence of serious risk would need to exist for a reclassification of the type suggested to occur. Only anecdotal reports of mild irritation have been offered in the submission. This is not extraordinary evidence ergo the reclassification should be refused.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Portugal		Individual	29
Comment received				
PG is considered only a mild irritant with very little to no known toxicity.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	Canada		Individual	30
Comment received				
I was a 40+ year smoker and have been smoke/tobacco free for over a year now thanks to vaping a new innovation that vaporizes PG with nicotine and inhaled. Even my doctor says I have made a wise choice to use vaping instead of tobacco. Why don't you all just admit that it is not about health but about the money and human life is worth less than the money! Hitler got people to do terrible things but in the end it was not just Hitler held accountable, how do you want your legacy remembered?				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Germany		Company-Manufacturer	31
Comment received				
As a manufacturer handling large amounts of PG as main solvent for flavourings, we point out that the reference to electronic cigarettes is possibly a current political issue, not necessarily a scientific one. This report unfortunately brings the known dihydrogenmonoxide hoax to our minds. For decades aerosols of 1,2 Propanediol are used in large scale and no harm, but only minor and negligible acute effects were barely reported. Not a single case of proven serious acute or even minor medium or long term effects on human health is known or cited, though a massive exposition to the world population exists for decades (several megatonnes per year!). Taking up on the reference to e-cigarettes and pointing out upcoming EU and especially German regulations on e-cigarette products, a classification would probably inadvertently but effectively ban (!) such products in Germany, if not the EU. Please also note in this context, that the proposal does NOT present the usage of the substance correctly. PG is widely used in food, cosmetics including lubricants, pharmaceutics and also large scale for veterinary germicides, pet food and tobacco, but also as deicing fluid for cars and aircraft. The list of usages is highly extensive, yet the proposal does not consider these massive scale usages properly. Instead, it references e-cigarette use and use for artificial fog in theatres only. Risks to human health resulting from usage rather than scientific substance properties are to be regulated separately and are not subject for classification. As a classification may not only ban e-cigarette products, but probably also would affect other unmentioned and yet unthought-of products and industries, opposed to the presented unproven minor acute and temporary symptoms shown in the proposal we'd like to escalate that massive and hard scientific proof should be applied first before a classification is viable. The Proposal, though, mainly conjectures. It especially fails to prove irritation and mistrades symptoms similar to those of irritations with irritations itself as intended by CLP regulations and is based on an ambiguous single study about 27 subjects which also not properly excludes external influences, while all other studies cited turn out to be clearly irrelevant. The proposal bases on rumour, internet sources provided by lay persons and isolated studies probably drawn a bit out of their context. A classification would have massive regulatory effects for this substance (megatonnes, see above) which are not justified by such weak evidence. Hence we request to reject the proposal until further major and significant scientific evidence is available.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number

10.03.2016	Germany	Eliquidlounge Alexander Bendschneider	Company-Downstream user	32
Comment received				
Our organisation disagrees with the proposed classification.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	33
Comment received				
Propylene Glycol is one of the ingredients in my heart spray so i can't see it being harmful.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2016	Netherlands	Propylene Oxide and Propylene Glycol Consortium	Industry or trade association	34
Comment received				

April 12, 2016
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).

A 5% decrease in FEV1, 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. 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.

Most importantly, there is no description of any associated inflammatory cell response in the nasal mucosa. 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. 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/m3) 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/m3 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/m3 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/m3 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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ECHA note - The following attachment was submitted with the comment above: *Final POPGs REACH Consortium com on PG CLP Proposal*

Dossier Submitter's Response
RAC's response

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2016	Belgium		Individual	35
Comment received				
No substantial scientific proof can be made that propylene glycol is carcinogenic in nature, nor can it be proven anecdotally that it has lasting adverse effects on the respitory system.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number

24.03.2016	Belgium		Individual	36
Comment received				
NO TOXIC				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Germany		Individual	37
Comment received				
I am vaping pure propylene glycol for almost 2 years now: I am healthier than ever and I was not even getting a flue or cold at any time during the last year. PG is absolutely safe to inhale!				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	38
Comment received				
No evidence has been offered in submission or can be found in the literature.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Portugal		Individual	39
Comment received				
PG isn't recognized as carcinogenic by the scientific community.				
Dossier Submitter's Response				
RAC's response				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2016	Belgium		Individual	40
Comment received				
Propylene Glycol has been widely used in medicinal applications as an antibacterial suspension, among those applications are medicinal inhalers with anti bacterial properties, deep cleansing solutions, et cetera.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Belgium		Individual	41
Comment received				
NO TOXIC				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Germany		Individual	42
Comment received				
I am vaping pure propylene glycol for almost 2 years now: I am healthier than ever and I was not even getting a flue or cold at any time during the last year. PG is absolutely safe to inhale!				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	43
Comment received				
No evidence has been offered in submission or can be found in the literature.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Portugal		Individual	44
Comment received				
PG isn't recognized as having any kind of relevant mutagenicity by the scientific community.				
Dossier Submitter's Response				
RAC's response				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Belgium		Individual	45
Comment received				
NO TOXIC				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Germany		Individual	46
Comment received				
I am vaping pure propylene glycol for almost 2 years now: I am healthier than ever and I was not even getting a flue or cold at any time during the last year. PG is absolutely safe to inhale!				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	47
Comment received				
No evidence has been offered in submission or can be found in the literature.				
Dossier Submitter's Response				

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Portugal		Individual	48
Comment received				
PG isn't regarded as toxic by the scientific community.				
Dossier Submitter's Response				
RAC's response				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2016	Belgium		Individual	49
Comment received				
Glycol based solutions have been used since the early 1960's in several applications directly influencing the respitory tract, such as fogmachines. While arguments can be made that prolonged exposure can lead to mild irritation of the respitory tract and eyes, lasting damage has only been recorded in few cases with prior known illness.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Belgium		Individual	50
Comment received				
NO TOXIC				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
24.03.2016	Belgium	UBV-BDB	National NGO	51
Comment received				
Le propylène glycol est utilisé comme solvant pour la cyclosporine dans une préparation pharmaceutique utilisée pour le traitement de patients suite à une transplantation pulmonaire (voir les références en bas de page). Je me demande pourquoi cette				

information (assurément scientifique) n'est pas citée dans la proposition. Au fait - les spray à la nicotine (Nicorette, QuickMist) utilisent aussi du propylène glycol comme solvant pour la nicotine.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Germany		Individual	52
Comment received				
I am vaping pure propylene glycol for almost 2 years now: I am healthier than ever and I was not even getting a flue or cold at any time during the last year. PG is absolutely safe to inhale!				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2016	Sweden		Individual	53
Comment received				
Consider the use of PG in currently existing, and approved, pharmaceutical preparations where a mist is sprayed into the oral cavity - it is outright silly to claim a compound with a long history of safe use is toxic by single exposure.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	Canada		Individual	54
Comment received				
Preclinical safety evaluation of inhaled cyclosporine in propylene glycol http://www.ncbi.nlm.nih.gov/pubmed/18158714 2.Lung deposition and pharmacokinetics of cyclosporine after aerosolization in lung transplant patients. http://www.ncbi.nlm.nih.gov/pubmed/12636164 3.Safety and toxicology of cyclosporine in propylene glycol after 9-month aerosol exposure to beagle dogs http://www.ncbi.nlm.nih.gov/pubmed/21476863				

4.Lung Deposition and Pharmacokinetics of Nebulized Cyclosporine in Lung Transplant Patients - 2014 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4088352/
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
10.03.2016	Germany	Eliquidlounge Alexander Bendschneider	Company-Downstream user	55
Comment received				
The presented scientific evaluation data lacks any significance: - Obviously a double-blind study does not exists. - The number of tested individuals is far too low. - The group of tested individuals cannot be considdered as representative. - Most reported effects are subjectiv impressions of the tested individuals. Conclusion: As long as a stastistic significance cannot be proofed, all data must be considdered as "hearsay".				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2016	United Kingdom		Individual	56
Comment received				
Please note that these comments are place under 'respiratory sensitisation' since there is no comment box available for 'respiratory irritation'. The main cited study 'of concern' is that of Wieslander (2001) (page 24) where a number of volunteers were exposed to artificial smoke (MPG mist) in an aircraft simulator. This is the only study used by the proposer to compare with the criteria for human evidence and without it there is no case to answer. It is therefore worth considering this study in more detail. In the interests of balance and assuming that most member states will not have time to refer to the original paper, I have included here more detail from it to put the information into better context since the results described in the proposal are merely a reproduction of the publication abstract. Wieslander raises the important question of what is meant by 'irritation'. It is frequently used to describe annoyance and discomfort and this needs to be quite clearly separated				

from physiological irritative response (as the classification criteria makes quite clear.) Note that the author indicates this by describing symptoms of annoyance as ocular and throat irritation. It should also be noted that symptoms were self-reported and the study was not blind so positive bias in the results cannot be excluded. The range of concentrations exposed to (nominally a single one but quite varied) was 176-851mg/m3. These exposures can only be described as very high.

The only significant subjective respiratory 'irritation' effects were throat dryness (17/23 of volunteers exposed) and an irritative cough (6/25), although it is worth noting that 2 of these 6 individuals reported these symptoms before exposure. Of all the other 6 types of nasal, throat or respiratory symptoms assessed, effects were only seen in 1 or 2 individuals out of the 27 volunteers exposed.

Of the objective measures assessed, there were no changes to the rhinometric parameters. For lung function, there was no significant change to vital capacity, forced vital capacity (FVC), peak expiratory flow and forced expiratory flow in one second (FEV1). The ratio of FEV1 to FVC decreased from an average of 86.8 (SD=7.3) to 84.8 (SD=6.3) and was reported as just reaching statistical significance (p-0.049). However, this minor change is very unlikely to have any biological relevance.

On the basis of a more objective consideration of the Wieslander publication, it is worth reviewing its content against the classification criteria because the comments of the classification proposer do not seem to be born out by the contents of the source document:

(a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair
function with symptoms such as cough, pain, choking, and breathing difficulties are included. This
evaluation will be based primarily on human data;

Evidence: A limited number of volunteers in Wieslander coughed but this was probably as a consequence of throat dryness in turn almost certainly due to the hygroscopic nature of MPG at the very high exposure. There is NO evidence in this publication of pain, choking, breathing difficulties, or true respiratory irritation (as opposed to discomfort) characterised by localised redness, oedema, pruritis and/or pain.

(b) 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);

Evidence: Contrary to what is reported in the proposal document on page 26, the Wieslander study DOES NOT show any evidence that these criteria are fulfilled. The rhinometric parameters assessed showed no change following exposure. The lung function parameters showed no significant changes either. There was a small change in one parameter, and whilst just statistically significant, this change is so minor in absolute terms it cannot be regarded as a biologically effect. Even the classification proposer describes the change as mild and there is no indication in the classification guideline that mild changes in a single parameter are sufficient to warrant classification!

(c) the 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, and dryness, which are outside the scope of classification for respiratory irritation; Evidence: In the Wieslander publication, none of the assessed parameters except the single reported effect of 'throat dryness' were seen in a significant number of the exposed volunteers. All other effects seen in single individuals can be dismissed as not being typical of an exposed population. The criteria indicate that reports of dryness are outside the scope of classification for respiratory irritation. In conclusion there is nothing in the Wieslander publication that remotely suggests effects that meet the criteria for classification as a respiratory irritant. The remaining presented data can be dismissed as best as equivocal or ambiguous or just plain irrelevant and there is no credible scientific evidence to support classification of MPG as a respiratory irritant.
Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	Germany		Individual	57
Comment received				
The German Bundesamt für Risikobewertung declared Propan-1,2-diol safe in theater fog. Even normal fog and high humidity can cause respiratory sensitation See 4.2.2. http://www.bfr.bund.de/cm/350/aerztliche_mitteilungen_bei_vergiftungen_1997.pdf				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Germany	Günther Schaidt SAFEX-CHEMIE GMBH	Company-Downstream user	58
Comment received				
The significance of the symptoms described in the study is low and they depend almost exclusively on subjective, by measurement not verifiable, personal feelings, different from				

what is shown in the proposal.
So the alleged reduction of the FEV 1 value after exposure of 103 % to 102 % is e. g. ranking in the area of uncertain measurement and is therefore scientifically irrelevant. (See page 8 of the Safex-rejection request)

The Animal experiments cited as supporting evidence are lying in an extremely high dose range while showing minimal health problems / changes in laboratory animals, so the use of PG as a constituent of Theatre fog fluids in the concentrations expected there, that are lower by several orders of magnitude than in the animal experiments, do not support any reason to suspect and it is extremely unlikely that the adverse effects described in the animal experiments will occur in humans, also especially because of the much shorter exposure times they were given.

A misclassification / unjustified marking with warnings is due to the psychosomatic potential that theatrical fog is known for, is counter-productive and would lead to nocebo-effects and self-fulfilling prophecy, this is just to be avoided.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Portugal		Individual	59

Comment received

PG is only considered as mildly irritant by the scientific community, excluding very rare cases of personal sensitivity to the said substance.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2016	Germany		Company-Manufacturer	60

Comment received

Aerosols of 1,2-Propanediol produce clearly visible, white "clouds", opposed to the expected fine grained fog of nonhygroscopic aerosols, which indicates the presence of water. This is expected, as 1,2-Propanediol is known to be quite hygroscopic.
Water is proven to have irritating effects on the eye, for example, also respiratory irritations are proven to occur from its aerosols when salt and/or ph value differ (yet one would not think of classifying water as STOT nevertheless).
Hence, one should also consider the main irritating factor of subtance aerosols possibly could be indeed water and not necessarily the substance itself. The Proposal presented no evidence.

No studies were provided by the proposal showing clear proof of the substance itself having respiratory SENSITISATION effects, only temporary minor effects are presented,

which mainly result from the hygroscopic nature of PG. Especially no consideration of air humidity was made and presented. Local dehydration unter dry air conditions is to be expected and mispresented in the report. In fact, when air humidity is high, the same substance is expected to have the opposite effect and moisturize human tissue, in analogy to other hygroscopic substances like 1,2,3-Trihydroxypropane.
The effects described are to be considered negligible and temporary. The hygroscopic property does not justify a STOT classification - it is not related to toxicity, nor are its effects severe enough.

The proposal cites reports of a few individuals on the internet. That is all but scientific or significant.
The report does not clearly separate aerosols from substance vapour.
The supportive studies are mainly insignificant (for example, PG is known to be toxic to cats and dogs, no relevance to humans).
As to the human effects, the proposal bases on a study (Wieslander et al) mainly, a supportive study on paint(!) and a NTP report about theatrical fog and actors.
The latter is insignificant, because "The dossier submitter noted that [...effects] were not attributable to propane-1,2-diol alone" (page 22), also in this NTP report significant effects were only achieved by extreme doses - and dosage was not scientifically specified ("5 times the broadway average is... what? except "massive"?)
The paint study is insignificant, because of the following citation from its summary: ""a study on painters[...] supports the thesis[!] that PG has an irritation effect on the mucosa of the upper airways. Due to the mixed exposure to different components emitted[,...] the findings cannot[!] be associated with PG[...]" (Page 20).
The main study the proposal bases (Wieslander et al) on
- was made in an aircraft simulator. Which we would expect to have air condition, hence extremely dry air, supporting the symptoms described (we also suspect the study to mainly aim at the bacteriostatic properties of PG, the respiratory effects probably being a side element to estimate impact on passengers). Lacking a high moisture cross study no evidence can be derived.
- was made with 22 men and 5 women, which is not representative,
- resulted finding only 4 subjectes reporting "development of irritative cough DURING EXPOSURE[!] to PG" - again, if you look at the summary table on page, under high doses (520 mg/m3, though in table 10 the range is noted up to 851mg/m3). DURING exposure, to be noted. Meaning it immediately stopped when exposure ceased.
Besides the fact that the subject count is not representative, this main study resulted basically in "throat dryness" and "nasal lavage" as the main effects on SOME of the subjects - which, unlike the proposal assumes on page 26, is not covered by the CLP regulations criteria for respiratory irritant effects ("redness, oedema, pruritis and pain"), even when the symptoms (mainly throat dryness) are somewhat NEAR the exampled symptoms (cited "cough, pain, choking and breathing difficulties). The main criteria is "impairing function". Proven impaired function to human beings in general, not only a few. A few could be also caused by allergic effects or anything else. Additionally, an irritation by aerosols immediately ceasing when exposure ends should not be considered for classification, because an aerosol simply brings small drops into the respiratory system which are to be considered foreign objects and hence WILL cause symptoms, disregarding the substance involved. The measured medical data could possibly also result from the body reaction to such foreign objects and the symptoms themselves, again not necessarily related to the substance.
The study is not significant, it not even fully supports the thesis.
We expect the same study with different substances, probably including water, usually will come to the same results.

The proposal does not show significant "hard" scientific proof, it bases on rumour and mainly isolated or interrogative studies, out-of-context irrelevant studies or studies not providing viable facts. It's pure speculation, it does not even make ANY assertion (and lets the reader draw his conclusions).
In fact, no scientific evidence is contained, but scientific speculations.

As to the substance itself, we refer to
- Murman, P (1984), "Prüfung der akuten Augen- und Schleimhautreizwirkung von 1,2-Propylenglykol" (Huels study no 0212) which covers mucosal irritation,
- Robertson, Loosli, Puck et.al "Test for chronic toxicity of propylene glycol on monkeys and rats by vapor inhalation and oral administration", J.Pharmacol.Exp.Therap 91:52-76, showing no acute effects (though local infections found after months of permanent high saturation exposure, which may or may not be related)

Our experience as commercial user of the substance is that under dry air conditions some few persons suffer minor, immediate acute irritations due to local dehydration that could be easily reverted by moisturizing (carefully inhaling water vapour or drinking a glass of water). A correlation to substance vapour cannot be made safely. Clearly visible and high doses of aerosol are needed for such symptoms to occur.

Undoubtly due to the hygroscopic nature of Propylene Glycol it may under some circumstances cause immediate acute, but minor and temporary, easily reverseable effects on mucosal tissue leading to similar symptoms like real irritations. (sore feeling, coughing - if you get anything but air into your lungs you cough, that's natural and - usually- totally unrelated to the substance involved). The proposal, though, does not provide anything but a thesis.

Given the massive impact on several industries, the weak evidence mainly showing only the hygroscopic properties but no "hard" toxicologic data, and regarding the negligible effects in terms of safety and human health, the report does not present enough scientific evidence to justify a classification of 1,2-Propanediol as proposed.

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2016	United Kingdom		Individual	61

Comment received

No strong evidence has been offered in submission other than anecdotal reports of mild airway irritation when PG is dispersed from theatrical fog machines. This is at odds with an overwhelming preponderance of evidence from studies of electronic cigarettes in which, despite deep exposure on a regular basis, airway irritation is rare, non-acute and has no permanent effect on spirometry. For example see Polosa et al (2014) for evidence of spirometry improvements is asthmatic smokers who switch to electronic cigarettes http://www.mdpi.com/1660-4601/11/5/4965

Dossier Submitter's Response
RAC's response

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	United Kingdom	Xyfil Ltd	Company-Downstream user	62

Comment received

1. Refers to Part A, 2.1 & 2.4
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
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
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 (FEV1) 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
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 FEV1 (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 FEV1 is not a clear indicator of the respiratory tract irritation. Thus, conclusion of the dossier submitter that this slight decrease in FEV1 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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Wieslander G, Norbäck D, and Lindgren T, 2001, Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects, OCCUPATIONAL & ENVIRONMENTAL MEDICINE. 58, pp 649-655.

Please note that the attachment has the same information as presented here, however, only the formatting is different to highlight different parts of the document such as sections, references.

ECHA note - The following attachment was submitted with the comment above: *Response to consulation on CLH report for PG 20.04.2016*

Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	Sweden		MemberState	63
Comment received				
The Swedish CA supports classification of Propane-1,2-diol (PG) in STOT SE 3, H335. Our opinion is that the human data on irritation fulfills the criteria for classification in STOT SE 3 for respiratory tract irritation, based on subjective measurements of respiratory irritation and objective measurements of lung effects after controlled exposure to PG mist, with support from evidence on respiratory irritation in theatrical workers exposed to artificial smoke containing glycols, including PG. The human data is also supported by findings of irritation as indicated by nasal haemorrhage (without histological changes in the trachea, lungs or larynx) in S-D rats during repeated exposure to low levels of PG aerosol. The relevance of the findings from the short term/acute toxicity studies used as supportive evidence in the CLH-proposal, i.e. increased release of mucous and degenerated goblet cells in rabbits (Konradova et al. 1978), bleeding around the eyes and nose of rats 7 days post exposure (Werley et al. 2011) and adverse behavior of Beagle dogs (Werley et al. 2011), is difficult to assess due to the lack of information on LC50 for PG. Hence, it is impossible to know how close the tested dose levels of PG are to the lethal concentrations of the substance. We note that this issue is not discussed in the CLH-report.				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	Belgium	The Electronic Cigarette Industry Platform on REACH ("eCIP")	Industry or trade association	64
Comment received				
Human data • The CLH report identifies Wieslander et al, 2001 as the key study. Limitations of the study include: • A lack of analytical characterization and purity information on the test substance • Exposure conditions simulating aviation emergency training, i.e. very short and extremely high exposures, not representative of the anticipated public and occupational exposure conditions from theatrical fog and electronic cigarettes cited as the justification for why action is needed at a community level • A study population of only 27 volunteers • The investigation was not a controlled exposure chamber test and exposures varied in an unexplained way between 171 mg/m3 up to 851 mg/m3. The classification criteria for respiratory tract irritation, (STOT SE 3) as set-out in Annex I - 3.8.2.2.1. to CLP are mainly based on human evidence of respiratory tract irritation that impairs function (emphasis added).				

In section 4.3.2 of the CLH report, the dossier submitter concluded that "the criteria for STOT SE 3 (respiratory tract irritant) are fulfilled". The dossier submitter justified its interpretation with the fact that throat dryness reported in Wieslander's study "indicates irritation of the upper respiratory tract and cough, mild airway obstruction and mild dyspnoea indicate impaired function of the lower respiratory tract". It also considered that "the slight reduction of forced expiratory volume in one second (FEV1) indicates slightly impaired lung function".
However, the data as presented in the article does not suggest a clinically relevant impairment of function: "Most of the lung function values remained unchanged after exposure to propane-1,2-diol, but there was a minor numerical decrease of FEV1 from 103% to 102% at exposure, and a small but significant decrease of FEV1/FVC (p=0.049). Mean VC was unchanged after the exposure, whereas FVC was slightly increased (table 4). None of the 27 participants had an initial lung function value (FEV1) below 80% of predicted value, but one got a 77% value for FEV1 after the exposure. The mean decrease of FEV1 and FEV1/FVC was similar in subjects with and without a history of atopy. Moreover, there were no significant association between a decrease in FEV1, and development of mild dyspnoea (measured by the rating scales) in the total material."
Further, according to the ECHA Guidance on the Application of the CLP criteria (version 4.1, June 2015 (hereafter referred to as "The Guidance"), for classification of a substance as a respiratory tract irritant, (STOT SE 3), "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, and dryness, which are outside the scope of classification for respiratory irritation".
The slight throat dryness reported in the Wieslander's study is a harmless and reversible short term sensation, and explains the observation of coughing without sore throat in 4 of the 27 individuals assessed. As per the classification criteria, coughing is only a relevant symptom for STOT SE 3 classification when it is a marker of impaired function, not as an end point on its own.
Slight airway obstruction was reported with no significant association with decreased lung function (forced expiratory volume in 1s, FEV1) (Wieslander et al., 2001). Where this effect was observed (in 4 volunteers) it was mild and only one participant had FEV1 below 80% of predicted value after exposure, and even that was 77%.There was thus no clinically relevant decrease in lung function.
Propane-1,2-diol is known to be hygroscopic, and this function contributes to the absorption of moisture from its surroundings. It is, in fact, used as a humectant, and moisturizer (Werley et al, 2011).
The hygroscopic nature of propane-1,2-diol explains the sensation of throat dryness reported in the Wieslander study. The ECHA Guidance on the CLP criteria notes that "The generic term RTI covers two different effects: 'sensory irritation' and 'local cytotoxic effects'. Classification in STOT-SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects."
Therefore, according to the CLP criteria, the sensation of throat dryness should not be considered for the classification as STOT SE 3 (respiratory tract irritation).
Second, The Guidance also clarifies that "the 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".

Wieslander's study was conducted on only 27 people. Of these, 6 were smokers and 12 were ex-smokers. In addition, 30% of the subjects exhibited a history of atopy. Thus, the majority of the study subjects were individuals potentially more sensitive to respiratory tract irritation due to their life-style (smokers) or medical "history". In addition, the authors reported a formaldehyde contamination of the test environment, which may have

contributed to the subjects' reported irritation.

• In Moline's study (Moline et al., 2000) quoted in the CLH report, actors were exposed to various theatre fogs generated from mixtures of glycols. No effect could be solely attributed to propane-1,2-diol.

The results of Wieslander and Moline are therefore questionable because in both instances, the study design was flawed. Also in the European Medicines Agency (EMA) report on "Background review for the excipient propane-1,2-diol", none of these studies were taken into consideration (CHMP, 2013).

• The Wieslander & Nörback study (2010) was also referenced as a supporting study in the CLH report however this study has also shortcomings since the study subjects (painters) were exposed to mixtures containing propane-1,2-diol and therefore the observed effects cannot be attributed to propane-1,2 –diol. Further, the study subjects had been exposed to the mixtures repeatedly over long periods of time. Therefore the study could not distinguish between potential single exposure effects and chronic effects from the repeated exposures. Effects from repeated exposures should not lead to STOT SE3 classification.

Animal studies
• In the 90-day sub-chronic nose inhalation study carried out by Suber (Suber et al., 1989), Sprague-Dawley rats were exposed to high concentrations of propane-1,2-diol (2-10 times higher than the 1 min. exposures in Wieslander's human study). In both exposed and control groups, no difference was observed in respiratory rates, minute volumes, tidal volumes, or breathing behaviour, indicating an absence of acute tract irritation. There were no histological changes in the trachea, lungs or larynx.

• A 28-day inhalation rat study (Werley et al., 2011) showed no adverse effect after continuous daily exposures to propane-1,2-diol at a level of 30,000mg/m3 up to 120 minutes per day. In addition, no macroscopic and histopathological findings were observed in respiratory tract of rats after inhaling propane-1,2-diol up to 41,000mg/m3 for 7 days.

In conclusion, propane-1,2-diol did not cause adverse effects up to the highest dose tested (CHMP, 2013).

Furthermore, nose bleeding and minimal laryngeal squamous metaplasia reported in rat inhalation studies are common local effects observed and are mostly species-related (Renne et al., 2007). Furthermore, they were not observed in dogs (Werley et al., 2011). Therefore, these effects are considered as irrelevant for assessing the systemic toxicity effect for propane-1,2-diol (CHMP, 2013).

• Konradova et al (1978) was also considered as supporting evidence for irritation effects however the test dose was extremely high and certainly not relevant for human exposure. Further, even with the high doses applied, the effects were mainly limited to mucus secretion. Indeed, the test dose was reported to be 10% but there was no indication of whether this concentration is expressed by weight or by volume. If the dose is expressed by volume, 10% would equate to a concentration of 335mg/L. If it were a w/w%, this would equate to 129mg/L and to put those concentrations into perspective, the higher propane-1,2-diol concentrations used in the 1 minute mist exposures study of Wieslander et al (2001) was averaged 520mg/m3, i.e. 0.5 mg/L. Exposures in the rabbit study were thus more than 250 times higher than the clinical study and stretched over a much longer period (20 and 120 minutes, versus 1 minute). Further, as noted in the CLH report,

measurements of propane-1,2-diol in air samples collected from theatrical smoke were less than 2.1mg/m3, i.e. 0.002 mg/L in the NIOSH, 1992 report, and maximum short-term exposure concentrations of four combined glycols were in the range of 0.37 – 46mg/m3 in Moline et al (2000), i.e. up to 0.05 mg/L. Exposures in the rabbit study were thus more than 2,800 times the maximum levels measured for the occupational actor scenario claimed to be of concern in the CLH report.

Self-classification and structural analogues
As indicated in our general comments, the third key point considered by the dossier submitter to justify the STOT SE 3 H335 classification of propane-1,2-diol is that "several" notifiers used STOT SE 3 in the self-classification, whereas "the majority of notifiers proposed no self-classification at all."

In this context we moreover had a look on several ECHA registered substances which we consider close enough to propane-1,2-diol, and thus suitable for grouping strategy approach. The twelve substances are listed in a table, provided as a separate attachment (Annex I), with respect to their classification as STOT SE3 H335.

Of the twelve structural analogues, nine do not have a single notifier supporting STOT SE3 H335. Of the remaining three, butane-1,3-diol is the worst case with still only 3% of notifiers proposing STOT SE3 H335. Overall, the evaluation of the classification data available from the ECHA CLP inventory for propane-1,2-diol (0.16% notifiers supporting STOT SE3 H335) in addition to the evaluation of STOT SE 3 H335 classification data from a series of similar substances, does not provide any supportive evidence that would justify the classification as proposed in the CLH dossier on propane-1,2-diol submitted to ECHA.

In conclusion, the material used as evidence in the dossier submitted by the German Federal Institute for Occupational Safety and Health (BAuA) does not support the proposed classification of propane-1,2-diol for respiratory tract irritation. eCIP members therefore disagree with the CLH proposal for propane-1,2-diol which is not supported by the BAuA dossier.

References

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ECHA note - The following attachment was submitted with the comment above: *Annex I to eCIP comments HCL proposal PG final 21042016*

Dossier Submitter's Response

RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
21.04.2016	United Kingdom	Independent British Vape Trade Association	Industry or trade association	65

Comment received

The reasons why we consider this CLH report inappropriate are explained in detail below.
Remarks in regards to animal studies
The CLH report stated that, there is no fully reliable animal study on acute irritation effects on the respiratory tract. And that all animal studies in the report (except the Suber study) had major limitations in assessing the effects on the respiratory tract tissues. Additionally, the microscopic examinations of the respiratory tract were lacking or incomplete (in particular for the nose). These studies are not reliably used as supportive evidence for specific target organ toxicity – single exposure.
In the Suber study[1] (1989), groups of nineteen Sprague-Dawley rats of each sex were exposed by a nose-only inhalation to 0.0, 0.16, 1.0 or 2.2 mg propylene glycol/litre air, for 6 hr/day, 5 days/wk for 90 days. There were no significant differences in respiratory rates, minute volumes or tidal volumes between any of the groups during aerosol exposure. The study did not demonstrate any systemic toxicity. The only biologically relevant findings were a significant increase in the number of goblet cells (a type of secretory cell found in the top layer of the intestinal and respiratory tract that secretes mucus) and/or an increase in the mucin content of the existing goblet cells in the nasal passages of rats exposed to the high and medium doses. In addition, the PG concentration in this study caused nasal haemorrhage and ocular discharge in a high proportion of animals; all of these reversible effects are considered to be the result of dehydration of the nares and eyes.
The authors attributed the observed nasal haemorrhage and ocular discharge to dehydration by PG of the nasal passage and eyes. The dehydration would be expected with PG, as it is a hygroscopic material and can cause irritation simply by removing excess water from the eyes and nasal passages.

The study by Robertson and colleagues[2] (1947), on primates exposed to 1g propylene glycol vapour for 12 to 18 months, found no evidence of toxicity on any organ (including the lungs) after post mortem examination of the animals. The study was performed in rats and monkeys and did not observe treatment related effects on respiratory physiology, clinical chemistry, haematology, gross pathology or respiratory tract histology. Monkeys and rats were continuously exposed to PG supersaturated vapour in chambers for 12 to 18 months at the following concentrations: rats, 0.17 to 0.35 mg/l (53 to110ppm) for 18months; monkeys 0.23 to 0.35 mg/l (72 to 110ppm) for 12 months. There was no sign of eye irritation in any of the exposed animals. No generalised or local inflammation of the bronchi or lungs was observed. Similar observations were seen in the study conducted by Werley et al.[3] , (2011) in rats and dogs.

Remarks in regards to human studies

The proposal for the classification and labelling of PG as STOT SE 3, is based mainly on one human study in which 27 volunteers were exposed to propylene glycol mist for 1 minute in an aircraft simulator under training conditions[4]. Exposures were high, ranging from 176 to 851 mg/m3 (mean = 309 mg/m3). Four volunteers who developed a cough exhibited evidence of airway obstruction as indicated by a 5% decrease in forced expiratory volume in 1 second (FEV1), while the rest did not exhibit any change in FEV1. The authors reported throat dryness in 64% of volunteers and impairment of respiratory function, proven by subjects (16% of volunteers) with cough, mild airway obstruction and mild dyspnoea.

It should be noted that, the study showed upper airways irritation but it is not clear if irreversible effects will occur. No permanent lung injury or long term health implication were detected from this study. The exposure concentration of PG (geometric mean 309 mg/m3) was quite high, compared with other exposure measurements of this compound in work environments. It is not clear if the effects seen in this study would be observed at a lower dose or in real life experience. The number of participant (n=27) in this study is very small. In addition, a few (4 out of 27) reacted with cough and slight airway obstruction and the exposure time (1 minute) is relatively short, giving the study limited power. Another limitation in this study is that, irritant respiratory effects were self-reported by volunteers, therefore there was an existence of an assessment bias as the study was not performed in double-blind conditions.

A Health Hazard Evaluation (HHE) on occupational exposure to propylene glycol during aircraft deicing operations was conducted by NIOSH[5]. Evaluation of deicing procedures was conducted at the Denver International Airport (DIA) in March 1996. At DIA, United Airlines uses a 50% solution of propylene glycol in water, heated to 180° F for deicing aircraft. Trucks with dual 800-gallon tanks, spray hoses, and booms are used. The amount of fluid used for deicing each plane ranges from 50 to 200 gallons. Personal breathing-zone air samples were collected from six ground sprayers, one basket man, and one truck driver. Air samples were collected on XAD-7 OVS tubes at a flow rate of 0.5 L/min for 6 hours and analyzed by GC/MS for propylene glycol according to NIOSH Method 5523. Seven workers had a range of exposures from 10 to 21 mg/m3 with a mean of 15 mg/m3, based on a 6-hour collection. The author concluded that "there was no hazard from overexposure to deicing fluid .Airborne exposure to propylene glycol was low and propylene glycol has low toxicity."

The study on painters by Wieslander & Norback [6] (2010) using water based paints, which is used as supportive evidence in the CLH report cannot be used to judge the irritancy potential of PG. In these studies painters were exposed to formulations containing several microbial volatile organic compounds including PG. The studies revealed irritative effects on the eyes and nasal mucosa. Associations were observed between measured exposure and biomarkers. And a significant correlation of 0.37 was found for PG and eosinophilic cationic protein from nasal lavage. The report clearly indicated that these findings were not observed in the study by Ernstgard et al.[7],

(2007) which included a 4-h exposure to a mixture of volatile organic compound including 10mg/m3 of PG. It is not clear if PG contributed to the irritative effects observed in these studies due to the mixed exposure to different components emitted from the water based paints.
The CLH report also used the NIOSH study that investigated the health effects associated with the use of theatrical smokes as supporting evidence[8]. In these investigations, air samples collected yielded propylene glycol concentrations < 2.1 mg/m3. However, there was a significant ($p<0.05$) increase in the reporting of respiratory irritant symptoms such as runny nose, stuffy nose, and sneezing by personnel from productions using theatrical smoke. It is unknown to what extent glycol vapors are present in theatrical fogs. Some of the constituents of theatrical "smoke," such as the aerolized glycols and mineral oil, could have irritative or mucous membrane drying properties in some individuals. Therefore propylene glycol cannot be identified as the only cause of the irritation observed.

In a study by Cohen and Crandall[9] (1964), fifty patients, 42 men and 8 women, of ages 18 to 71 years, with chronic bronchitis, bronchial asthma, and chronic diffuse obstructive pulmonary emphysema, had pulmonary function studies performed before and immediately after a 15-minute inhalation of isoproterenol-HCl, a sympathomimetic drug with bronchodilator properties, in a super-heated mixture (“Thermo-Fog”) of 40 percent propylene glycol in isotonic saline. Vital capacity, F.E.V.1 maximum minute ventilation, vital capacity time and Breathing Reserve Ratio were the indices chosen for examination. This therapy resulted in a significant enhancement of the average maximum minute ventilation and shortening of the vital capacity time, with less definite effects upon the group average vital capacity, breathing reserve ratio and timed 1-second vital capacity values. Sixty percent of the patients showed individual vital capacity rises and 72 percent had individual rises in maximum minute ventilation figures. There were no adverse clinical effects and the aerosol was well tolerated. The super-heated aerosol, generated by a simple and inexpensive device, appears to be a suitable vehicle for administration of a bronchodilator drug.
In a series of experiments to control airborne infections, over 105 children were subjected to bactericidal concentrations of propylene glycol in the wards of a children’s convalescent home in experiments conducted over 3 years[10]. Six wards of the Children’s Seashore House in Atlanta containing 105 bedfast children aged 3 to 15 years were divided into 3 control and 3 undergoing vaporization for 3 week periods with 2 to 3 days between, before the control wards become vaporized, and the vaporized wards became controls. This rotation continued for 7 months. The PG was heated to vaporize it, but not above 80 degrees C, and vaporization continuously maintained a concentration of 0.069 mg per liter. (0.07 ppm). No ill effects were reported. In the first year, 100 infections occurred in control wards without PG, and 5 in wards with PG vaporization, with rates of 0.18 per week and 0.09 per week respectively. Most of the upper respiratory infections in control wards were common colds, suggesting the PG is also virucidal. Hence, exposure of children to PG at 94 mg/m3 caused no effects on respiratory mucous membranes.
A recent review by the European Medicines Agency on the excipient propylene glycol, used in medicinal products as a co-solvent in aerosols (10 - 25%) was published in 2014[11]. The inhalation route of exposure was considered and the expert committee concluded on the safe incorporation of propylene glycol in pharmaceutical preparations. However, the review by the Expert Committee did not make mention of the Wieslander study in humans on which the proposal for the classification and labelling as STOT SE 3 is mainly based.
Conclusions
Studies on the irritant and respiratory effects of occupational exposure to air borne PG are not available.
The animals studies presented in the CLH report, assessing the adverse respiratory effects after acute or intermediate inhalation exposure of animals to propylene glycol are

inconclusive. These studies do not indicate a basis for concern because comparable exposure conditions do not occur for the general population.
Both the study on painters using water based paints and the studies that investigated the health effects associated with the use of theatrical smoke, used in this report as supporting evidence are limited in scope.
As indicated earlier, the exposure concentration of PG (geometric mean 309 mg/m3) used in the key study was quite high. In the study by Suber et al., 1989, the nasal haemorrhage and ocular discharge due to dehydration of the nasal passages and eyes was observed at a high concentration of 160 mg/m3 of a fine aerosol of PG (median aerodynamic diameter of around 2µ). By comparison, the highest air concentration in the NIOSH study of theoretical fog was less than 2mg/m3. Furthermore, the NIOSH study in which workers were exposed to propylene glycol during aircraft deicing operations at concentrations up to 21mg/m3 revealed no effects. In the study conducted by Harris and Stoke 1945, exposure of children to PG at 94 mg/m3 caused no effects.
The NTP 2004 report[12] stated that, of an average of 263 mL of nebulized aerosol, 8.1 mL containing 10% propylene glycol was retained per hour, corresponding to about 0.8 g of compound, which in turn amounts to 0.09 g/kg per 8 hours. Therefore, it can be concluded that under normal conditions of exposure, propylene glycol via inhalation is of limited toxicological relevance.
In conclusion, except for the amount of PG entering the nasopharynx and being swallowed, under normal exposure conditions PG exposure by inhalation is not toxicologically relevant due to its low vapour pressure (0.07 mm Hg). Thus, a classification and labelling of PG as STOT SE 3, is not warranted.

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Dossier Submitter's Response
RAC's response

Date	Country	Organisation	Type of Organisation	Comment number
20.04.2016	United Kingdom	JTI SA	Company-Manufacturer	66

Comment received

JTI comment on 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, this non-classification was challenged and a new proposal for Harmonized Classification and Labelling was submitted to European Chemicals Agency (ECHA) by the German Federal Institute for Occupational Safety and Health (BAuA). In their proposal, the BAuA suggested to classify propane-1,2-diol as respiratory tract irritant (STOT SE 3).
The proposal for STOT SE 3 (RTI) classification is mainly based on one publication (Wieslander G et al., 2001), where the authors investigated the effects of the acute exposure to propane-1,2-diol mist on 27 non-asthmatic volunteers in a flight simulator. Wieslander G et al., concluded that the short exposures (1 min) to propane-1,2-diol at 309 mg/m3 (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." The study was conducted on a limited number of subjects (n=27), where 8 subjects had history of atopy, hay fever or history of childhood eczema and more than a half of the subject were either current or ex-smokers. According to the authors, 100% of those with atopy but only 28% of those without reported development of throat symptoms (mainly dryness) and 4 subjects developed irritative cough after exposure to propane-1,2-diol mist.
Additionally, no significant changes were detected in any measurements of nasal patency and most of the lung function values remained unchanged after exposure.
Propane-1,2-diol is used as a humectant in broad variety of consumer products, drugs and medical devices as a carrier of active substances. It is well known to have hygroscopic properties and therefore, the inhaled particles take up moisture as they traverse the upper respiratory airways. Due to these properties it may cause occasional throat dryness and mild cough, which was reported by Wieslander G et al., 2001.
According to the CLP regulation "respiratory irritant effects are characterised by localised 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 G et al., (2001) did not report any evidence of respiratory tract redness, oedema, and inflammation or breathing difficulties, in addition, the study is of limited

power and there was no air control group.
As supporting studies, BAuA cited several acute and short-term studies in rabbits, rats and Beagle dogs (Konradova et al., 1978; Suber et al., 1989; Werley et al., 2011).
Konradova et al., (1978) used only 6 rabbits, divided into 2 groups, where one was exposed to 10% propane-1,2-diol for 20 minutes and the second one for 2 hours. 20-minute exposure induced minimal ultrastructural changes of the trachea (small apical cytoplasmic blebs) and the signs of pathological alterations (cytoplasmic protrusions with destruction of kinocilia) were only observed after 2-hour exposure. No other observations were reported.
In Werley et al., (2011) publication, 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." Additionally, in dogs, no histopathological effects on the laryngeal, tracheal and lung tissues were observed.
Suber et al., (1989), reported that after 13-week nose-only inhalation exposure to propane-1,2-diol rats did not display any significant changes in respiratory rates, tidal volumes or minute volumes in comparison to the control group. An increase in the number of goblet cells or increase in mucin content of the goblet cells was observed in the nasal turbinates of both male and female rats. This changes appeared to be due to hygroscopic properties of propane-1,2-diol. Similarly, nasal hemorrhaging in animals exposed to higher concentrations of propane-1,2-diol can be explained by its dehydrating effects on peripheral tissues.
BAuA also cited a report, prepared on the request of Actors' Equity Association and the League of American Theaters and Producers (Moline et al., 2000), in which authors investigated the irritant effects of theatrical fog. The study was conducted over 2 years with 439 actors, however, the fog was a mixture of several glycols, and therefore, no effect could be attributed exclusively to propane-1,2-diol.
Furthermore, BAuA in their proposal mentioned numerous internet forums indicating that the inhalation of propane-1,2-diol vapor caused sore throat, mucus membranes irritation, wheezing and coughing in users of e-cigarettes or persons exposed to the theatrical fog. Such internet information does not represent reliable data source for the classification and labelling process since it is impossible to determine the exact exposure of the consumers and the purity of propane-1,2-diol.
Conclusion
JTI disagrees with the proposal of the BAuA to classify propane-1,2-diol as STOT SE 3 (respiratory tract irritant).
BAuA has based their proposal mainly on a single study that has been conducted on only 27 human subjects, among them 8 had a history of atopy, hay fever or childhood eczema. Similarly, the supporting animal studies used by BAuA did not show any histopathological changes in the larynx, trachea and lungs related to exposure to propane-1,2-diol.
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 throat dryness and mild cough, which are transient and reversible effects.
In conclusion, JTI is of the opinion that the current CLP classification of propane-1,2-diol is appropriate and that scientific evidence does not support its classification as suggested by the BAuA.

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ECHA note - The following attachment was submitted with the comment above:
JTI_PG_CLP

Dossier Submitter's Response
RAC's response

NON-CONFIDENTIAL ATTACHMENTS

1. *Annex I to eCIP comments HCL proposal PG final 21042016*. Submitted on 21/04/2016 by The Electronic Cigarette Industry Platform on REACH ("eCIP"). [Please refer to comments No 11, 64]
2. *Final POPGs REACH Consortium com on PG CLP Proposal*. Submitted on 18/04/2016 by Propylene Oxide and Propylene Glycol Consortium. [Please refer to comment No 34]
3. *Fontem Ventures - Comments on CLP Report - Proposal for Harmonised Classification and Labelling.* Submitted on 21/04/2016 by Fontem Ventures. [Please refer to comment No 23]
4. *JTI_PG_CLP.* Submitted on 20/04/2016 by JTI SA. [Please refer to comment No 66]
5. *PG_STOTSE3_com_FIVAPE.* Submitted on 22/04/2016 by FIVAPE / Fédération Interprofessionnelle de la Vape. [Please refer to comment No 9]
6. *Response to consulation on CLH report for PG 20.04.2016.* Submitted on 21/04/2016 by Xyfil Ltd. [Please refer to comment No 62]

CONFIDENTIAL ATTACHMENTS

1. Commentaires suite à la proposition pour le CLP de modification de classification de la substance PG. Submitted on 21/04/2016 by GAIATREND. [Please refer to comment No 5]