



# Risicoschatting van de shisha-pen

## Introductie

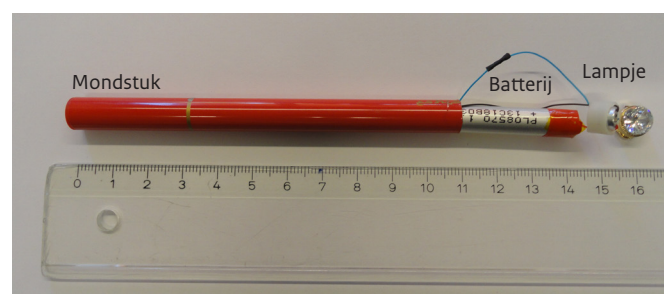
Een shisha-pen is een elektronische waterpijp, in de vorm van een pen en verkrijgbaar in allerlei kleuren en smaken, zoals aardbei, vanille en cola. Een shisha-pen is wegwerpbaar of oplaadbaar en navulbaar en is verkrijgbaar met of zonder nicotine. Shisha-pennen worden verkocht via internetwinkels en zijn verkrijgbaar in winkels waar ook tabakswaar wordt verkocht (Trimbos-instituut, 2013). Er is veel ophef over de shisha-pen ontstaan sinds in de media gerapporteerd is dat deze populair zou zijn onder basisschoolleerlingen (De Gelderlander 2013). De shisha-pen zou mogelijk de werking van een 'oefensigaret' hebben waardoor de drempel voor het roken van tabak wordt verlaagd. VWS heeft daarom het RIVM gevraagd om de mogelijke risico's van het gebruik van de shisha-pen in kaart te brengen (Ministerie van VWS, 2013). Het RIVM kijkt in deze analyse naar de chemische productveiligheid van de shisha-pen. De eventuele sociaal-maatschappelijke risico's, zoals het aanzetten tot het roken van tabak, zijn in dit onderzoek niet meegenomen.

Voor deze risicoschatting heeft het RIVM verschillende smaken (appel, aardbei, druif) van een veel verkochte, wegwerpbare shisha-pen zonder nicotine geanalyseerd.

## Werking van de shisha-pen

Een shisha-pen is een pen met aan het ene uiteinde een lampje in de vorm van een diamant en aan het andere uiteinde een mondstuk met gaatje. Het omhulsel bevat een elektrisch circuit met batterij en een spiraaltje dat via een touwtje gekoppeld is aan een gaasje doordrenkt met vloeistof. Door te zuigen aan het mondstuk, wordt het elektrisch circuit gesloten en gaat de shisha-pen 'aan'. Hierdoor licht het lampje op en wordt het spiraaltje warm. Zodra het spiraaltje verwarmd wordt, verdampt de vloeistof in het touwtje, waardoor witte rook ontstaat. Deze damp, of rook, wordt ingeademd. Door te stoppen met zuigen, wordt het elektrisch circuit onderbroken. Het lampje gaat uit en het spiraaltje koelt af.

De Shisha-pen is klaar voor de volgende 'trek', totdat alle vloeistof uit het gaasje via het touwtje verdampt is.



# Risicoschatting

## Samenstelling van de damp

De hoofdbestanddelen van de damp die wordt geïnhaald na het nemen van een trekje van de shisha-pen zijn propyleenglycol (54%) en glycerol (46%). Dit is vastgesteld door het RIVM laboratorium. Daarnaast bevat de damp een kleine hoeveelheid smaakstof en mogelijk sporen van andere stoffen (<1%). De damp van een elektronische sigaret (e-sigaret) bevat kleine hoeveelheden schadelijke stoffen, zoals aldehydes. De aanwezigheid van aldehydes in de damp van de shisha-pen is door het RIVM uitgesloten. Naar de aanwezigheid en karakterisering van sporen van andere bestanddelen heeft het RIVM niet gekeken. De risicoschatting zal zich richten op de hoofdbestanddelen, propyleenglycol en glycerol, in de damp van de shisha-pen.



Propyleen glycol in namaakrook (© Afbeelding: Federal Office of Public Health FOPH, Zwitserland)



Glycerol in zeep. (© Afbeelding: Federal Office of Public Health FOPH, Zwitserland)

## Achtergrond

Propyleenglycol wordt toegepast in de voedings-, cosmetische, farmaceutische en kunststofindustrie. Het wordt eveneens gebruikt om de namaakrook en mist te creëren die vaak in discotheken, theaters en televisieproducties wordt gezien (RIVM, propyleenglycol). Glycerol wordt gebruikt in veel verschillende

industriële en consumentenproducten, zoals zeep en schoonmaakmiddelen, medicijnen, cosmetica, voedingsmiddelen, verf, hars en papier (RIVM, glycerol). Beide stoffen worden veilig beschouwd indien gebruikt als additief in voedingsmiddelen (FDA, GRAS Substances (SCOGS) Database). Anders dan bij gebruik in voedingsmiddelen, worden propyleenglycol en glycerol via de shisha-pen ingeademd, wat leidt tot blootstelling van de luchtwegen en longen. Van propyleenglycol is bekend dat herhaaldelijke, kortdurende blootstelling aan ogen, huid, neus en mond irritatie kan veroorzaken (ATSDR, 1997).

## Scenario in shisha-pen

De fabrikant rapporteert dat van de shisha-pen tot wel 500 hijsen genomen kunnen worden (productverpakking shisha-pen). Dit is bevestigd door het RIVM. Daarnaast heeft het RIVM bepaald wat de concentratie van propyleen glycol en glycerol is in de damp van de shisha-pen die geïnhaald wordt bij het nemen van één trekje. Deze concentraties zijn het gemiddelde van vier shisha-pennen (2 aarbei, 1 appel, 1 druif). Met deze gegevens heeft het RIVM voor beide stoffen een risicoschatting gemaakt. Details van deze risicoschatting worden beschreven in het technische document in de bijlage van deze factsheet (appendix: technical document risk assessment of propylene glycol and glycerol in the shisha-pen (English)).



Shisha-pen met appel

Er wordt daarbij rekening gehouden met de concentratie van de stoffen die na het nemen van een hijs wordt bereikt in de luchtwegen (RIVM, 2012). Voor de shisha-pen is het nog onbekend hoeveel trekjes een gebruiker per tijdseenheid neemt, wat het volume is van de damp die geïnhaald wordt, en hoelang één sessie van gebruik gemiddeld duurt. Daarom is uitgegaan van scenario's die beschreven zijn voor de e-sigaret (Etter, 2010; Etter en Bullen, 2011) en de "gewone" sigaret (Djordjevic, 2000). Het RIVM heeft twee scenario's vergeleken, een scenario van 28 trekjes in 12 minuten en een minimaal scenario van het nemen van één trekje. Uit de berekeningen van het RIVM blijkt dat de concentratie van propyleenglycol en glycerol die bereikt wordt in de luchtwegen en longen nauwelijks verandert wanneer wordt uitgegaan van deze verschillende scenario's.

Voor de risicoschatting worden de concentraties die bereikt worden in de luchtwegen en longen na het gebruik van een shisha-pen vergeleken met gegevens uit gepubliceerde studies. Er is gezocht naar studies die het meest vergelijkbaar zijn met de scenario's waarin gebruikers worden blootgesteld aan de damp

van de shisha-pen. In de risicoschatting is rekening gehouden met de verschillen tussen de studies en de werkelijke situatie, zoals verschil in duur van de blootstelling en verschil in organisme als het om studies in proefdieren gaat.

## Risico van inhaleren van propyleenglycol damp

De hoeveelheid propyleenglycol aanwezig in de damp die wordt ingeademd na het nemen van één trekje is hoog genoeg om irritatie van de luchtwegen te veroorzaken. Dit is gebaseerd op een studie met proefpersonen die kortdurend (één minuut) werden blootgesteld aan propyleenglycol damp uit een rookmachine (Wieslander *et al.*, 2001). In deze studie ondervonden alle proefpersonen irritatie van de luchtwegen (droge keel, hoesten) bij lagere concentraties dan die bij blootstelling aan één trekje van de shisha-pen. De effecten van langdurige blootstelling aan propyleenglycol via de shisha-pen kunnen moeilijk geschat worden, omdat gegevens over langdurige blootstelling van mensen ontbreken. Wel is bekend dat bij ratten die langdurig worden blootgesteld aan propyleenglycol, de dikte van het luchtweg-epitheel en de slijmproductie in de luchtwegen toenemen (Suber, 1989). De concentratie propyleenglycol die bereikt wordt in de luchtwegen en longen na het nemen van één trekje van de shisha-pen is hoger dan de aanbevolen maximale concentratie in namaakrook en mist uit rookmachines voor, onder andere, theaterproducties (Toxnet).

## Risico van inhaleren van glycerol damp

De hoeveelheid glycerol aanwezig in de damp die wordt ingeademd na het nemen van één trekje kan irritatie van de luchtwegen (droge keel, hoesten) veroorzaken. Voor glycerol zijn er geen gegevens bekend van kortdurende blootstelling in mensen. De conclusie is daarom gebaseerd op een studie in ratten (Renne, 1992). Deze studie laat zien dat glycerol, in concentraties die lager zijn dan die na het nemen van één trekje van de shisha-pen, door irritatie veranderingen veroorzaakt in het epitheel van het strotklepje. Omdat onbekend is hoe de shisha-pen gebruikt wordt en omdat er onvoldoende vergelijkbare studies beschikbaar zijn, is niet duidelijk of vergelijkbare effecten ook op kunnen treden na langdurig gebruik van de shisha-pen.

## Risico van inhaleren van de damp uit een shisha-pen

De risicoschatting is gebaseerd op blootstelling aan propyleenglycol en glycerol afzonderlijk. Over het effect van blootstelling aan beide stoffen tegelijk, zoals het geval is bij het inhaleren van de damp uit de shisha-pen, zijn geen gegevens bekend. Ook is het onbekend wat de risico's zijn van de eventuele sporen van andere bestanddelen die geïnhaleerd worden via shisha-pen.

## Conclusie

Bij gebruik van de shisha-pen worden propyleenglycol en glycerol geïnhaleerd, wat leidt tot blootstelling van de luchtwegen en longen. Op basis van de risicoschatting kan worden geconcludeerd dat het nemen van één trekje van de shisha-pen voldoende is om de luchtwegen te irriteren (droge keel, hoesten). Of het gebruik van de shisha-pen zal leiden tot vergelijkbare effecten zoals gezien bij ratten, kan aan de hand van de huidige beschikbare gegevens niet geschat worden. Vooral omdat nog onbekend is hoe consumenten de shisha-pen precies gebruiken. Des te vaker en langduriger consumenten de shisha-pen gebruiken, des te groter is de kans op nadelige effecten op het luchtweg-epitheel.

## Bronvermelding

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## Appendix: technical document risk assessment of propylene glycol and glycerol in the shisha-pen (English)

A shisha-pen is an electronic inhaler that vaporises a liquid solution into an aerosol mist which simulates the act of tobacco smoking. Shisha-pens are available in disposable or rechargeable and refillable format. The liquid solution in both formats is available with or without nicotine.

An analytical analysis was performed by the RIVM to measure the major components in the liquid solution present in disposable shisha-pens without nicotine. The major components found in shisha-pens were propylene glycol (54%) and glycerol (46%).

We have no information on how young people use the shisha-pen (puffs per session, sessions per day, duration of use). Therefore, we can only make assumptions using the currently available data. Here we try to assess the possible risks by assuming that the smoking behaviour is like that of cigarette smoke (Djordjevic *et al.*, 2000) and that the sessions are like that of e-cigarettes. We assessed two exposure scenarios: 1-puff (a one-time exposure) and 28 puffs in 12 minutes (a continuous user, realistic worst-case) (<http://www.e-cigarette-forum.com/forum/ecf-library/26111q-tobacco-cigarette-vs-e-cigarette-nicotine-equivalency.html>).

The RIVM performed measurements of the concentration of propylene glycol and glycerol present in the smoke of shisha-pens (2 strawberry, 1 apple and 1 grape). The average level of propylene glycol was found to be 0.71 mg/puff (min 0.61, max 0.79 mg/puff) and the average level of glycerol was found to be 0.58 mg/puff (min 0.48, max 0.69 mg/puff). The total average level of both propylene glycol and glycerol in one puff was 1.29 mg (min 1.09, max 1.49 mg/puff).

The estimated maximum alveolar concentrations of propylene glycol in a 1-puff and 28-puff session were estimated to be 603 and 735 mg/m<sup>3</sup>, respectively. A study of volunteers (n = 27) exposed to propylene glycol for 1 minute at concentrations ranging from 176- 851 mg/m<sup>3</sup> showed upper airway irritation (Wieslander *et al.*, 2001). It is not clear if irreversible effects will occur but an animal study showed that repeated exposure (6 h per day; 5 days per week) for 90 days at 1000 and 2200 mg/m<sup>3</sup> caused irreversible respiratory damage (Suber *et al.*, 1989). Limits for propylene glycol by actors exposed via theatrical fog has been set at 40 mg/m<sup>3</sup> (ToxNet, 2013). The estimated maximum alveolar concentrations of propylene glycol in 1- or 28-puffs exceeds this peak acceptable concentration. This analysis of the shisha-pen demonstrates that **a risk of irritating effects on the respiratory tract epithelium due to propylene glycol exists.**

The estimated maximum alveolar concentration of glycerol in a 1-puff was estimated to be 495 mg/m<sup>3</sup>. There were no human inhalation studies with glycerol. Two animal studies showed that continuous exposure (6 h per day; 5 days per week) for 14 and 90 days showed irritation to the upper respiratory tract at 662 and 1000 mg/m<sup>3</sup>, respectively (Renne, 1992). Given the high inhaled concentration of glycerol in one puff, **a risk of irritating**

**effects on the respiratory tract epithelium due to glycerol exists with increased duration of shisha-pen exposure.**

Here we have performed a single-component analysis and the combined effects of propylene glycol and glycerol need further investigation. In addition, little information is known in regards to how young people use the shisha-pen (puffs per session, sessions per day, duration of use). More information to fill this data gap is needed to better assess the long-term risks of smoking shisha-pens.

## Harmful health effects of propylene glycol

### Hazard assessment of toxic effects

The direct toxicity of propylene glycol, toxicity due to its direct adverse effects, is described in this section.

### Carcinogenic effects

There is no evidence that propylene glycol is carcinogenic to humans (The Health Council of the Netherlands (2007)).

### Non-carcinogenic effects: Local respiratory effects and systemic effects

The main effects reported following propylene glycol exposure were an increased number of goblet cells in the respiratory tract and nasal hemorrhaging observed when rats were exposed to 160 mg/m<sup>3</sup> (the lowest concentration tested), 6 hours per day, 5 days per week for 13 weeks (Suber *et al.*, 1989). Effects such as nasal burning, stinging and throat irritation were attributed to exposure to propylene glycol as part of a pharmaceutical formulation inhaled by patients suffering from allergic rhinitis for 4 weeks. However, these effects were significantly less following a change in the content of propylene glycol in the formulation from 20% to 5% (HCN, 2007).

Non-asthmatic volunteers (n = 27) were exposed in an aircraft simulator to propylene glycol mist for 1 minute. Short exposure to propylene glycol mist from artificial smoke generators caused acute ocular and upper airway irritation in non-asthmatic subjects. A few (4 out of 27) reacted with cough and slight airway obstruction (Wieslander *et al.*, 2001).

Minor systemic effects were observed only in female rats which included body weight reduction and changes in leukocyte profile. These systemic effects on body weight and leukocyte profile have not been found consistently in other studies indicating that gender differences in susceptibility to propylene glycol's adverse effects in the rat, but other studies do not provide additional evidence for this (HCN, 2007).



## Risk assessment of local respiratory effects and systemic effects

In the absence of an appropriate Human Limit Value derived for the scenario of shisha-pen smoking the present procedure for risk assessment described herein is confined to a Margin of Exposure (MOE) approach, i.e. comparison of an appropriate toxicological Point of Departure (PoD) with the estimated human exposure. The MOE is evaluated given the necessary extrapolation steps involved whether clear conclusions can be drawn or if refinement is necessary. The latter is beyond the scope of the present fact sheet. Basic calculations and a detailed description of the exposure and risk assessment steps have been previously described by Bos et al. (2012).

### Scenario #1: 1-puff scenario

#### Step 1: Exposure assessment

For the exposure scenario, the same method as previously described (Bos et al., 2012) was utilized with a few adaptations. Puffing patterns (puff frequency, strength and duration) vary considerably among individuals who smoke electronic cigarettes or shisha-pens, but surveys indicate that individuals take an average of 120-175 puffs per day (Etter, 2010; Etter and Bullen, 2011). There is no data available on the duration of shisha-pen smoking sessions and therefore we can only assume that 1 puff has a volume of 50 mL (Djordjevic et al., 2000).

The average concentration per shisha-pen smoking session can be calculated by adapting the exposure scenario described previously for cigarette smoking (Bos et al., 2012) and dividing the amount in mg inhaled during a shisha-pen session ( $D_{1-puff\ shisha-pen}$ ) by 0.05L.

$$C_{alv,max} = 0.042 \times D_{1-puff\ shisha-pen} / 0.05 = 0.85 \times D_{1-puff\ shisha-pen} \text{ in mg/L}$$

Gas chromatography (GC) analysis performed in the RIVM showed that the smoke in the shisha pen was comprised of an average of 0.71 mg/puff of propylene glycol.

$$C_{alv,max} = 0.85 \times D_{1-puff\ shisha-pen} = 0.85 \times 0.71 \text{ mg} = 0.603 \text{ mg/L} = 603 \text{ mg/m}^3$$

The estimated inhaled concentration of propylene glycol per puff was 0.71 mg with a maximum alveolar concentration ( $C_{alv,max}$ ) of 603 mg/m<sup>3</sup>.

#### Step 2: Point of Departure

There were no toxicity studies that mimicked the exposure scenario of shisha-pen smoking. Therefore 1 human study in which humans were exposed to an aerosol mist as part of an aviation emergency training, and 1 animal study with repeated exposure for 6 h per day, 5 days per week, for 13 weeks were considered the best PoD values for further risk assessment. Please refer to Tables 1-2 for MOE calculation.

#### Step 3: Risk on local effects

The margin of exposure (MOE, ratio of toxicity point of departure/exposed concentration; the smaller the ratio, the higher the risk) for respiratory tract irritation was found to range from 0.3 to 1.4 (Tables 1-2). Factors to be taken into account for evaluation of this MOE included LOAEL as PoD

instead of NOAEL, difference in exposure pattern between human and/or animal experiment and daily use of shisha-pen, less-than-lifetime exposure, interspecies extrapolation (rat to humans), and interindividual variability.

Considering the MOE and the factors to be accounted for, it is concluded that a **risk of effects on the respiratory tract epithelium due to propylene glycol exists.**

**Table 1.** Summary of the study used as a PoD, the  $C_{alv,max}$  from amount of propylene glycol present in shisha-pens and the MOE analysis

Description	Selected study
Critical endpoint	Acute irritation of the eyes and upper airways A few (4 out of 27) individuals reacted with additional cough and slight airway obstruction
Source	The Health Council of the Netherlands (2007) (Wieslander et al., 2001)
Species	Healthy human subjects (27)
Exposure regimen	Propylene glycol in aviation emergency training. Exposure to artificial mist generator in short-term inhalation exposure (~1 min)
Concentrations tested (mg/m <sup>3</sup> )	0, 176-851
Duration of exposure	Average rating on 10 questions before and after 1 min propylene glycol exposure every 30 min for 4 hours
NOAEL (mg/m <sup>3</sup> )	-
If no NOAEL, then value for LOAEL	Min range = 176 Max range = 851 Mean range = 309
$C_{alv,max}$ (mg/m <sup>3</sup> )	603
Source of $C_{alv,max}$ (mg/m <sup>3</sup> )	1 puff (50 mL)
MOE <sub>1-puff shisha-pen/100% transfer rate</sub>	<b>Min range = 0.3 (~3x higher than in human study)</b> <b>Max range = 1.4</b> <b>Mean range = 0.5 (~2x higher than in human study)</b>

**Table 2.** Summary of the study used as a PoD, the  $C_{alv,max}$  from amount of propylene glycol present in shisha-pens and the MOE analysis

Description	Selected study
Critical endpoint	Increased number of goblet cells in the respiratory tract
Study	(Suber et al., 1989) <a href="http://www.atsdr.cdc.gov/toxprofiles/tp189.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp189.pdf</a>
Species	Rat
Exposure regimen	6 h per day, 5 days/week
Concentrations tested (mg/m <sup>3</sup> )	0, 160, 1000, 2200
Duration of exposure	13 weeks

Description	Selected study
NOAEL (mg/m <sup>3</sup> )	160
If no NOAEL, then value for LOAEL	1000
C <sub>alv,max</sub> (mg/m <sup>3</sup> )	603
Source of C <sub>alv,max</sub> (mg/m <sup>3</sup> )	1 puff (50 mL)
MOE <sub>1-puff shisha-pen/100% transfer rate</sub>	<b>NOAEL = 0.3 (~4x higher than animal study)</b> <b>LOAEL = 1.7</b>

It is recognised that several assumptions have been made and that the risk assessment can be refined reconsidering these assumptions. Although such a refinement is beyond the scope of the present analysis, considering the low MOE, it remains to be seen if further refinement will alter the conclusion.

## Scenario #2: 28-puffs in 12 minutes

### Step 1: Exposure assessment

For the exposure scenario, the same method as previously described (Bos *et al.*, 2012) was utilized with a few adaptations. The puffing patterns in shisha-pens were considered more similar to those found in e-cigarettes and not tobacco cigarettes. In general, a cigarette can be smoked in about 13 puffs (Djordjevic *et al.*, 2000) while with a shisha-pen, individuals can take as many puffs as desired with varying intervals between puffing bouts. Puffing patterns (puff frequency, strength and duration) vary considerably among individuals who smoke electronic cigarettes or shisha-pens, but surveys indicate that on average individuals take 120-175 puffs per day (Etter, 2010; Etter and Bullen, 2011). There is no data available on the duration of shisha-pen sessions but an estimate of 12-minute session has been suggested for e-cigarettes (<http://www.e-cigarette-forum.com/forum/ecf-library/26114-tobacco-cigarette-vs-e-cigarette-nicotine-equivalency.html>). Given the similarities between e-cigarettes and shisha-pen, we will use this estimate in our exposure scenario. Therefore, using our previous exposure scenario (puff volume, 50 mL; puff duration, 1.5 sec; puff interval 20 sec) (Bos *et al.*, 2012) we estimate 28 puffs per 12 minute session minutes (a continuous user, realistic conservative scenario).

It is assumed that the total of volume of these 28 puffs is 1400 mL (28 puffs x 50 mL per puff). The average concentration per shisha-pen smoking session can be calculated by adapting the exposure scenario described previously for cigarette smoking (Bos *et al.*, 2012) and dividing the amount in mg inhaled during a shisha-pen session ( $D_{28-puff\ shisha-pen}$ ) by 1.4 L.

$$C_{alv,max} = 0.052 \times D_{28-puff\ shisha-pen} / 1.4 = 0.037 \times D_{28-puff\ shisha-pen}$$

Gas chromatography (GC) analysis performed in the RIVM showed that the smoke in the shisha pen was comprised of an average of 0.71 mg/puff x 28 puffs = 19.88 mg of propylene glycol

$$C_{alv,max} = 0.037 \times D_{28-puff\ shisha-pen} = 0.037 \times 19.88\ mg = 0.735\ mg/L = 735\ mg/m^3$$

The estimated inhaled concentration of propylene glycol per 28-puffs was 19.88 mg with a maximum alveolar concentration ( $C_{alv,max}$ ) of 735 mg/m<sup>3</sup>.

### Step 2: Point of Departure

There were no toxicity studies that mimicked the exposure scenario of shisha-pen smoking. Therefore 1 human study of volunteers exposed to an aerosol mist used for aviation emergency training, and 1 animal study with continuous exposure for 6 h per day, for 5 days per week, for 13 weeks were considered the best PoD values for further risk assessment. Please refer to Tables 3-4 for MOE calculation.

### Step 3: Risk on local effects

The MOE for respiratory tract irritation was found to range from 0.2 to 1.4 (Tables 3-4). Factors to be taken into account for evaluation of this MOE included LOAEL as PoD instead of NOAEL, difference in exposure pattern between human and/or animal experiment and daily use of shisha-pen, less-than-lifetime exposure, interspecies extrapolation (rat to humans), and interindividual variability.

Considering the MOE and the factors to be accounted for, it is concluded that a **risk of effects on the respiratory tract epithelium due to propylene glycol exists**.

**Table 3.** Summary of the study used as a PoD, the  $C_{alv,max}$  from amount of propylene glycol present in shisha-pens and the MOE analysis

Description	Selected study
Critical endpoint	Acute irritation of the eyes and upper airways A few (4 out of 27) individuals reacted with additional cough and slight airway obstruction
Source	The Health Council of the Netherlands (2007) (Wieslander <i>et al.</i> , 2001)
Species	Healthy human subjects (27)
Exposure regimen	Propylene glycol in aviation emergency training. Exposure to artificial mist generator in short-term inhalation exposure (~1 min)
Concentrations tested (mg/m <sup>3</sup> )	0, 176-851 (personal exposure not measured)
Duration of exposure	Average rating on 10 questions before and after 1 min propylene glycol exposure every 30 min for 4 hours
NOAEL (mg/m <sup>3</sup> )	-
If no NOAEL, then value for LOAEL	Min range = 176 Max range = 851 Mean range = 309
C <sub>alv,max</sub> (mg/m <sup>3</sup> )	735
Source of C <sub>alv,max</sub> (mg/m <sup>3</sup> )	12 min session of 28 puffs (estimate)

Description	Selected study
MOE <sub>28-puff shisha-pen session/100% transfer rate</sub>	<b>Min range = 0.2 (~4x higher than in human study)</b> <b>Max range = 1.2</b> <b>Mean range = 0.4 (~2x higher than in human study)</b>

**Table 4.** Summary of the study used as a PoD, the  $C_{alv,max}$  from amount of propylene glycol present in shisha-pens and the MOE analysis

Description	Selected study
Critical endpoint	Increased number of goblet cells in the respiratory tract
Source	(Suber et al., 1989) <a href="http://www.atsdr.cdc.gov/toxprofiles/tp189.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp189.pdf</a>
Species	Rat
Exposure regimen	6 h per day, 5 days/week
Concentrations tested (mg/m <sup>3</sup> )	0, 160, 1000, 2200
Duration of exposure	13 weeks
NOAEL (mg/m <sup>3</sup> )	160
If no NOAEL, then value for LOAEL	1000
$C_{alv,max}$ (mg/m <sup>3</sup> )	735
Source of $C_{alv,max}$ (mg/m <sup>3</sup> )	12 min session of 28 puffs (estimate)
MOE <sub>28-puff shisha-pen session/100% transfer rate</sub>	<b>NOAEL = 0.2 (~5x higher than animal study)</b> <b>LOAEL = 1.4</b>

## Conclusion

Margin of exposure (MOE) analysis of the shisha-pen demonstrates that a **risk of irritating effects on the respiratory tract epithelium due to propylene glycol exists**. Propylene glycol has very low systemic toxicity in experimental animals and very high doses are used in most acute studies to determine a toxic level.

## Harmful health effects of glycerol

### Hazard assessment of toxic effects

The direct toxicity of glycerol, toxicity due to its direct adverse effects, is described in this section.

### Carcinogenic effects

No carcinogenic effects have been reported.

### Non-carcinogenic effects: Local respiratory effects and systemic effects

The main effects reported following glycerol exposure were local irritant effects to the upper respiratory tract observed when rats were exposed to 662 mg/m<sup>3</sup>, 6 hours per day, 5 days per week for 13 weeks, with no toxic effects observed at 165 mg/m<sup>3</sup> (Renne, 1992). No systemic effects were

reported in this study or in a study with rats exposed to concentrations of 1000, 1930 and 3910 mg/m<sup>3</sup>, 6 hours per day, 5 days per week for 14 days (Renne, 1992).

## Risk assessment of local respiratory effects and systemic effects

*In the absence of an appropriate Human Limit Value derived for the scenario of shisha-pen smoking the present procedure for risk assessment described herein is confined to a Margin of Exposure (MOE) approach, i.e. comparison of an appropriate toxicological Point of Departure (PoD) with the estimated human exposure. The MOE is evaluated given the necessary extrapolation steps involved whether clear conclusions can be drawn or if refinement is necessary. The latter is beyond the scope of the present fact sheet. Basic calculations and a detailed description of the exposure and risk assessment steps have been previously described by Bos et al. (2012).*

### Scenario #1: 1-puff scenario

#### Step 1: Exposure assessment

For the exposure scenario, the same method as previously described (Bos et al., 2012) was utilized with a few adaptations. Puffing patterns (puff frequency, strength and duration) vary considerably among individuals who smoke electronic cigarettes or shisha-pens, but surveys indicate that individuals take an average of 120-175 puffs per day (Etter, 2010; Etter and Bullen, 2011). There is no data available on the duration of shisha-pen smoking sessions and therefore we can only assume that 1 puff has a volume of 50 mL (Djordjevic et al., 2000).

The average concentration per shisha-pen smoking session can be calculated by adapting the exposure scenario described previously for cigarette smoking (Bos et al., 2012) and dividing the amount in mg inhaled during a shisha-pen session ( $D_{1-puff\ shisha-pen}$ ) by 0.05L.

$$C_{alv,max} = 0.042 \times D_{1-puff\ shisha-pen} / 0.05 = 0.85 \times D_{1-puff\ shisha-pen} \text{ in mg/L}$$

Gas chromatography (GC) analysis performed in the RIVM showed that the smoke in the shisha pen was comprised of an average of 0.582 mg/puff of glycerol

$$C_{alv,max} = 0.85 \times D_{1-puff\ shisha-pen} = 0.85 \times 0.58 \text{ mg} = 0.495 \text{ mg/L} = 495 \text{ mg/m}^3$$

The estimated inhaled concentration of glycerol per puff was 0.58 mg with a maximum alveolar concentration ( $C_{alv,max}$ ) of 495 mg/m<sup>3</sup>.

#### Step 2: Point of Departure

There were no toxicity studies that mimicked the exposure scenario of shisha-pen smoking. Two studies with continuous exposure were found. The first had an NOAEL of 165 mg/m<sup>3</sup> and a LOAEL of 662 mg/m<sup>3</sup> for local irritant effect to the respiratory tract in rats exposed 6 h per day, 5 days per week for 13 weeks (concentrations tested were 0, 33, 165 and 662 mg/m<sup>3</sup>) (Renne, 1992). Another study showed an LOAEL of 1000 mg/m<sup>3</sup> for local irritant effects of the upper respiratory tract in rats exposed 6 h per day, 5 days per week for 2 weeks (concentrations tested were 0, 1000, 1930 and

3910 mg/m<sup>3</sup>) (Renne, 1992). It must be kept in mind that the rat study used glycerol exposure for 6h per day, in comparison it to 1 puff of a shisha-pen.

### Step 3: Risk for local effects

Because a relevant study with a similar exposure pattern as that of a shisha-pen could not be found, a reliable MOE could not be calculated. Nevertheless, the inhaled concentration of glycerol in one puff was estimated to be 495 mg/m<sup>3</sup>, in comparison to an NOAEL of 165 mg/m<sup>3</sup>, and an LOAEL of 1000 and 662 mg/m<sup>3</sup> observed for local irritant effect in 2- and 13-week rat studies, respectively. Given the high inhaled concentration of glycerol in one puff, **a risk of irritating effects on the respiratory tract epithelium due to glycerol exists with increased duration of exposure.** Factors to be taken into account include difference in exposure pattern between animal experiments and daily use of shisha-pen, less-than-life-time exposure, interspecies extrapolation (rat to humans), and interindividual variability.

## Conclusion

The high concentration of inhaled glycerol in one puff of the shisha-pen demonstrates that **a risk of irritating effects on the respiratory tract epithelium due to glycerol exists with increased duration of exposure.**

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