**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)**

# Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Updated risk assessments for exposure of users to propylene glycol (PG) and glycerol from inhalation of E(N)NDS aerosols.

Updated risk assessment of Propylene Glycol and Glycerol using modelling approaches, provided by Dr. Tharacad Ramanarayanan and Dr. Doug Wolf

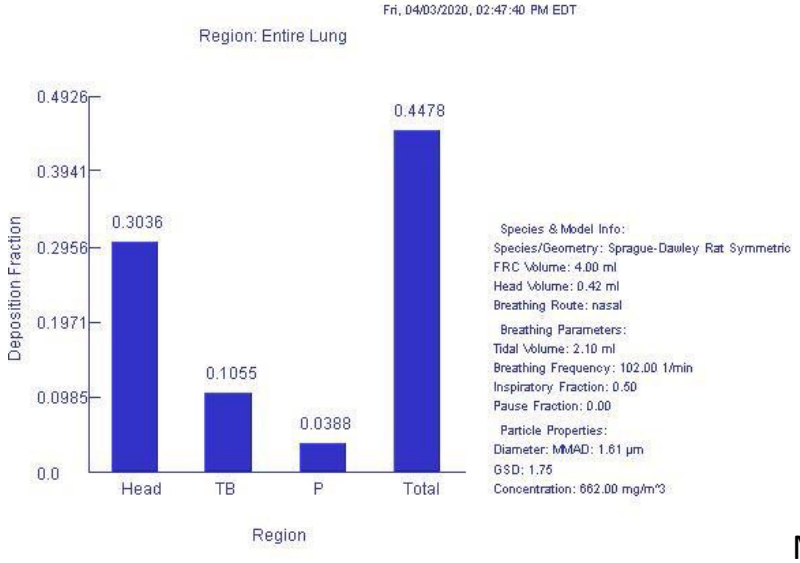
# Calculating Human Equivalent Concentration (HEC) and Human Equivalent Dose (HED) to Evaluate the potential for adverse health effects associated with exposure of users to propylene glycol (PG) and/or glycerol from use of electronic nicotine (and non-nicotine) delivery systems (E(N)NDS; e-cigarettes).

Tharacad Ramanarayanan and Doug Wolf

## Assumptions

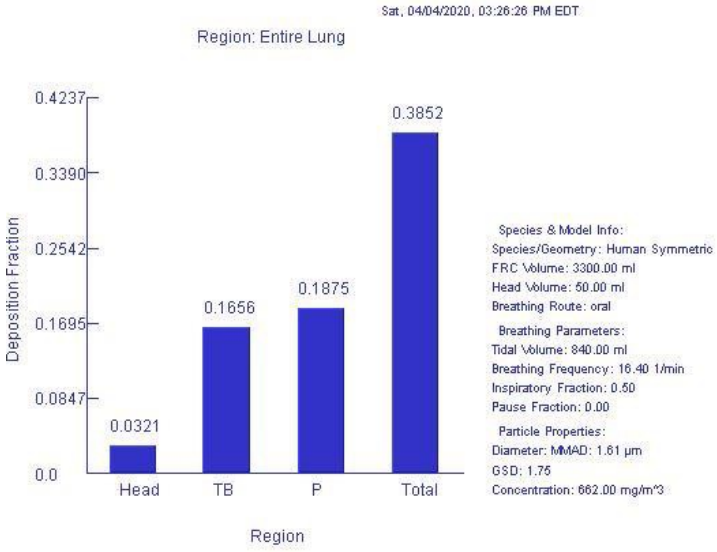
- Puffs per day = 300 (estimated using data from Dawkins et al. (2018))
- Period of vaping = 16 h (assuming 8 hours of sleep)
- Breathing Rate for Rat, $V_{E\text{-}rat}$ = 0.214 L/min (calculated from EPA (1994))
- Breathing rate for Human, $V_{E\text{-}human}$ = 13.8 L/min (EPA 1994)
- Tidal volume (L/breath) (EPA, 1994)
    - S-D Rat = 0.0021 L/breath
    - Human = 0.84 L/breath
- Breathing Frequency (breaths per min) – standard values (EPA 1994)
    - Rat = 102
    - Human = 16.4
- Surface Area – Tracheobronchial + Pulmonary Region (TB + P) (EPA 1994)
    - Human = 54.3 $m^2$
    - Rat = 0.3422 $m^2$

# ANALYSIS

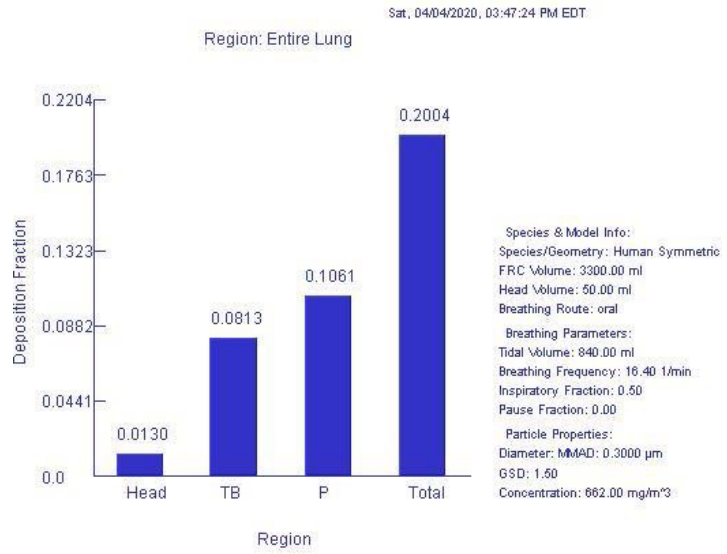



## MPPD OUTPUTS

MPPD Output for Fraction of Deposition in parts of the respiratory tract of Sprague-Dawley Rat for MMAD = 1.61 µm GSD = 1.75.




MPPD Output for Fraction of Deposition in parts of the respiratory tract of Human model for MMAD = 1.61 µm GSD = 1.75.




MPPD Output for Fraction of Deposition in parts of the respiratory tract of Human model for E(N)NDS with MMAD = 0.3 µm GSD = 1.5 (estimated from data in Pratte, Cosandey and Goujon-Ginglinger (2016)).

## DEPOSITION FRACTION – OUTPUT FROM MPPD

| | Deposition fraction (DF) | | | | |
|---|---|---|---|---|---|
| **Scenario** | Total | Head | TB | P | TB + P |
| **Rat nasal (MMAD: 1.61 µm; GSD: 1.75)** | 0.47 | 0.414 | 0.016 | 0.04 | 0.056 |
| **Human oral (MMAD: 1.61 µm; GSD: 1.75)** | 0.3852 | 0.0321 | 0.166 | 0.1875 | 0.3531 |
| **Human oral (MMAD: 0.3 µm; GSD: 1.5)** | 0.2 | 0.013 | 0.0813 | 0.1061 | 0.1874 |

## CALCULATING HEC AND HED

$$NOAEC_{adj} = NOAEC_{study} \times \left(\frac{H_r}{H_H}\right) \times \left(\frac{D_r}{D_H}\right) \times \frac{f_r}{f_H}$$

NOAECadj = NOAEC adjusted for study duration and Human Exposure duration (mg/L)
NOAECstudy = NOAEC from the rat study (mg/L)
$H_r$ = Hours per day – rat = 6h
$H_H$ – Hours per day – human (h) = 16 h
$D_r$ = Days of exposure per week - Rat
$D_H$ = Days of exposure per week – human
$f_r$ = fraction of time exposed to chemical (rat) = 1.0
$f_H$ = fraction of time exposed to chemical (human)

$$f_H = \frac{Number\ of\ puffs\ per\ day}{16\ hrs \times 16\ \frac{breaths}{min} \times \frac{60min}{hr}} = \frac{300}{15360} = 0.019$$

$$\mathrm{HEC} = \mathrm{NOAEL}_{\mathrm{adj}} \times \mathrm{DAF} \times \mathrm{PAF}$$

HEC = Human-Equivalent Concentration (mg/L)
$\mathrm{NOAEL}_{\mathrm{adj}}$ = duration-adjusted NOAEL (mg/L)
DAF = Dosimetry Adjustment Factor
PAF = Particle-size Adjustment Factor

$$\mathrm{DAF} = \left(\frac{V_E \times \mathrm{DF}}{\mathrm{SA}}\right)_{\mathrm{rat}} \div \left(\frac{V_E \times \mathrm{DF}}{\mathrm{SA}}\right)_{\mathrm{human}}$$

DAF = Dosimetry Adjustment Factor
$V_E$ = minute ventilation (L/min)
DF = deposition fraction in rat or human pulmonary region
SA = surface area of rat or human pulmonary system

$$\mathrm{DAF} = \left(\frac{0.214 \times 0.056}{0.3422}\right)_{\mathrm{rat}} \div \left(\frac{13.8 \times 0.3531}{54}\right)_{\mathrm{human}} = 0.388$$

$$\mathrm{PAF} = \frac{\mathrm{DF}_{\mathrm{human};1.61\,\mu\mathrm{m}}}{\mathrm{DF}_{\mathrm{human};0.3\,\mu\mathrm{m}}}$$

$\mathrm{DF}_{\mathrm{human;\ 1.61\ \mu m}}$ = deposition fraction of 1.61 µm (GSD=1.75) particle in human pulmonary region = 0.3531
$\mathrm{DF}_{\mathrm{human;\ 0.3\ \mu m}}$ = deposition fraction of 0.3 µm (GSD=1.5) particle in human pulmonary region = 0.1874

PAF = 0.3531 / 0.1874 = 1.884

## HEC Results

| Carrier | NOAEC or LOAEC (mg/L) | $\mathrm{NOAEC_{adj}}$ or $\mathrm{LOAEC_{adj}}$ (mg/L) | DAF | PAF | HEC (mg/L) |
|---|---|---|---|---|---|
| **PG** | 0.16 (LOAEC) | 2.26 ($\mathrm{LOAEC_{adj}}$) | 0.388 | 1.884 | 1.65 |
| **Glycerol** | 0.662 (NOAEC) | 9.33 ($\mathrm{LOAEC_{adj}}$) | 0.388 | 1.884 | 6.82 |

## Exposure and Risk Assessment

Dose per puff (from Margham et al. (2016))

PG -> 0.7 mg per puff

Glycerol -> 1.6 mg per puff

### Maximum (one puff) Concentration

$$\text{PG} = \frac{0.7}{0.84} = 0.83 \text{ mg/L}$$

$$\text{Glycerol} = \frac{1.6}{0.84} = 1.90 \text{ mg/L}$$

### Average Daily Concentration

Number of breaths per minute = 16

Total number of breaths per day = 16 × 60 × 24 = 23,040

Average tidal volume = 0.84 L

Total volume inhaled per day = 23040 × 0.84 = 19,353 L

$$\text{PG} = \frac{0.7 \times 300}{19353} = 0.011 \text{ mg/L}$$

$$\text{Glycerol} = \frac{1.6 \times 300}{19353} = 0.025 \text{ mg/L}$$

### Margins of Exposure

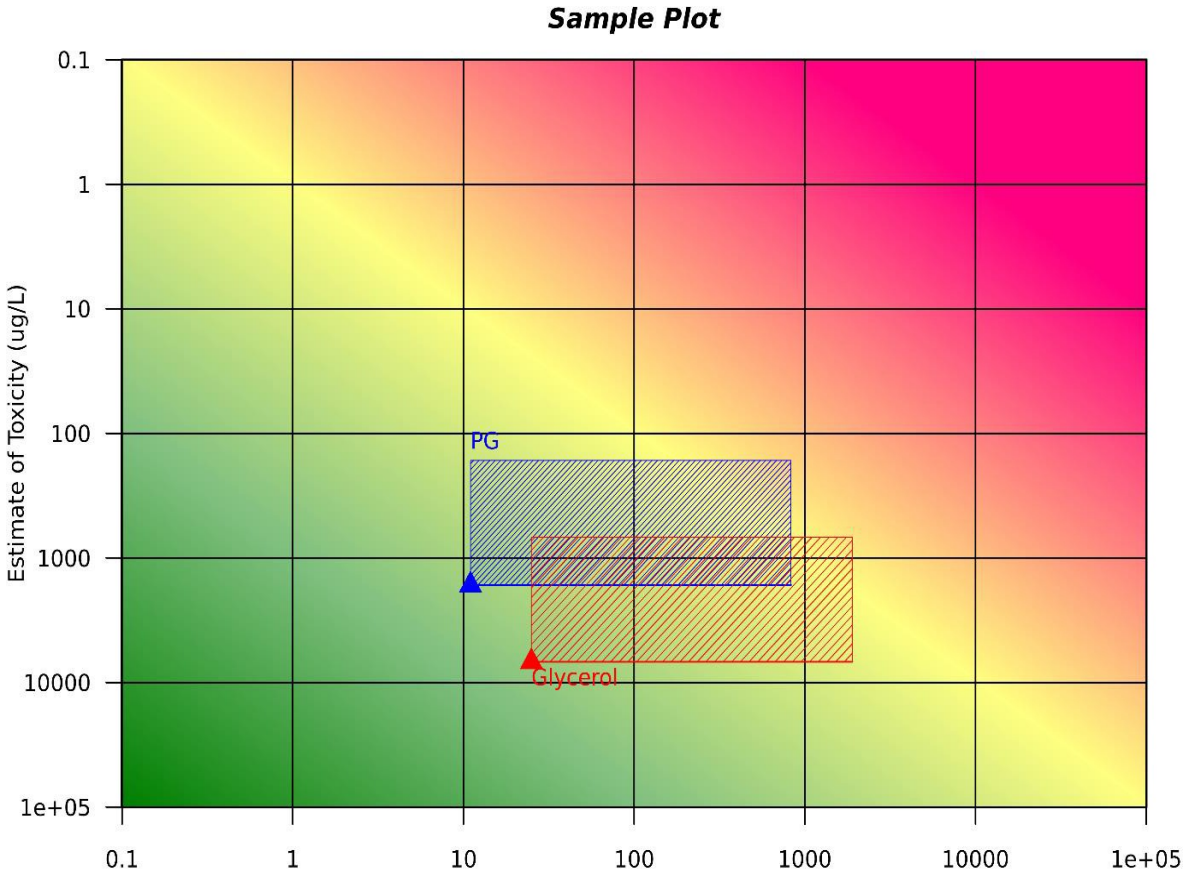
| **Carrier and Scenario** | **MOE calculation (HEC/exposure concentration)** | **MOE** |
|---|---|---|
| **PG – Max concentration in 1 breath** | 1.65/0.83 | 1.99 |
| **PG – Average daily concentration** | 1.65/0.011 | 150 |
| **Glycerol – Max concentration in 1 breath** | 6.82/1.90 | 3.59 |
| **Glycerol – Average daily concentration** | 6.82/0.025 | 273 |

## RISK21 PLOT

SAFETY FACTORS ASSUMED

**PG**: Interspecies – 3X; Intraspecies – 3X; Total = 10X

**Glycerol**: Interspecies – 3X; Intraspecies – 3X; Total = 10X



## RISK21 PLOT DATA (µG/L OR MG/M3)

| Name | Color | Line Type | Line Width | Density | Text Loc | Min Exp | Max Exp | Exp Point | Exp UF | Min Tox | Max Tox | Tox Pt | Tox UF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Propylene glycol | [automatic] | solid | thin | high | above-left | 11 | 830 | | | 1650 | 165 | 1650 | 10 |
| Glycerol | [automatic] | solid | thin | medium | above-left | 25 | 1900 | | | 6820 | 682 | 6820 | 10 |

**References**


Dawkins, L., S. Cox, M. Goniewicz, H. McRobbie, C. Kimber, M. Doig & L. Kosmider (2018) 'Real-world' compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. Addiction*,* 113**,** 1874-1882.

EPA. 1994. U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development. EPA/600/8-90/066F.

Margham, J., K. McAdam, M. Forster, C. Liu, C. Wright, D. Mariner & C. Proctor (2016) Chemical Composition of Aerosol from an E-Cigarette: A Quantitative Comparison with Cigarette Smoke. Chem Res Toxicol*,* 29**,** 1662-1678.

Pratte, P., S. Cosandey & C. Goujon-Ginglinger (2016) A scattering methodology for droplet sizing of e-cigarette aerosols. Inhalation toxicology*,* 28**,** 537-545.