

### Supplementary file 3: Margin-of-Exposure (MoE)

Table S3.1: MoEs at the median and maximum exposure concentration for each exposure scenario, based on reported PoDs and the concentrations in e-liquids according to EU-CEG

Substance name	NOAEL/BMDL ( $\mu\text{g}/\text{kg bw}/\text{day}$ )	Minimum MoE	Substance concentration in e-liquids according to EU-CEG (mg/mL)		Daily dose scenario 4 ( $\mu\text{g}/\text{kg bw}/\text{day}$ )				Daily dose scenario 3 ( $\mu\text{g}/\text{kg bw}/\text{day}$ )			
			Median	Maximum	Median	MoE	Maximum	MoE	Median	MoE	Maximum	MoE
2,3,5-Trimethylpyrazine	18000	400	0.16	23.29	16.46	1094	2328.77	<b>8</b>	4.55	3954	644.30	<b>28</b>
Tabanone	40000	1200	0.14	5.82	13.72	2916	582.19	<b>69</b>	3.79	10540	161.07	<b>248</b>
2-Ethyl-3-methylpyrazine	5200	400	0.01	0.40	0.60	8667	40.00	<b>130</b>	0.17	31325	11.07	470
<i>p</i> -Cresol	50000	400	0.00	0.14	0.30	168350	14.00	3571	0.08	608491	3.87	12909
(-)-Carophyllen oxide	109000	400	0.01	0.05	0.94	116453	5.10	21379	0.26	420912	1.41	77272
alpha-Angelica lactone	17400	400	0.00	0.02	0.14	121800	2.19	7931	0.04	440238	0.61	28665
5-(Hydroxymethyl)-2-furfural	14400	700	0.00	0.02	0.20	72120	1.76	8182	0.06	260674	0.49	29573

The MoEs in bold indicate a possible health risk for that scenario and concentration of the substance in e-liquids.

NOAEL = No-Observed Adverse Effect Level

BMDL = Bench Mark Dose Level

Table S3.1. continued

Substance name	NOAEL/BMDL (µg/kg bw/day)	Minimum MoE	Substance concentration in e-liquids according to EU-CEG (mg/mL)		Daily dose scenario 2 (µg/kg bw/day)				Daily dose scenario 1 (µg/kg bw/day)			
			Median	Maximum	Median	MoE	Maximum	MoE	Median	MoE	Maximum	MoE
2,3,5-Trimethylpyrazine	18000	400	0.16	23.29	1.99	9037	281.88	<b>64</b>	1.00	18075	140.94	<b>128</b>
Tabanone	40000	1200	0.14	5.82	1.66	24092	70.47	<b>568</b>	0.83	48184	35.23	<b>1135</b>
2-Ethyl-3-methylpyrazine	5200	400	0.01	0.40	0.07	71600	4.84	1074	0.04	143200	2.42	2148
<i>p</i> -Cresol	50000	400	0.00	0.14	0.04	1390836	1.69	29506	0.02	2781672	0.85	59011
(-)-Carophyllene oxide	109000	400	0.01	0.05	0.11	962084	0.62	176623	0.06	1924168	0.31	353245
alpha-Angelica lactone	17400	400	0.00	0.02	0.02	1006259	0.27	65520	0.01	2012518	0.13	131040
5-(Hydroxymethyl)-2-furfural	14400	700	0.00	0.02	0.02	595827	0.21	67595	0.01	1191654	0.11	135189

MoE was calculated by dividing the NOAEL or BMDL by the daily dose. A possible health risk could occur for cases where the calculated MoE was lower than the minimum MoE.

The minimum MoE was calculated according to commonly used assessment factors:

- For differences between species
  - Factor 10 for translation from rat to human
  - Factor 17.5 for translation from mouse to human
  - Factor 10 for interspecies differences
- For differences in exposure duration
  - Factor 6 for subacute (14 of 28 day studies) to chronic exposure
  - Factor 2 for subchronic (90 day studies) to chronic exposure
- For differences in exposure route
  - Factor 2 for oral studies to inhalation