Supplementary file 1: Exposure scenarios

The exposure scenario to determine daily e-liquid consumption was based on a previously published RIVM report (1), information from users fora (https://damp-e.nl/blog/hoe-lang-doe-je-met-een-flesje-e-liquid# , https://www.esigaretsolutions.nl/service/ , https://dampforum.nu/topic/9925-hoeveel-liquid-gebruik-je-ongeveer/ , consulted on 27th of January 2022), and data related to the use of e-liquid per puff as measured with a VC1 smoking machine and with a clearomizer (1,6 Ω, puff volume of 55 ml/puff, puff duration of 3 seconds). The average weight of e-liquid per puff was 12.41 mg.

The assumptions to determine the exposure of a user are:

- No pyrolysis occurs and no chemical reactions of the compounds in e-liquid occur. Currently data on such reactions is too limited for the chemicals listed to be considered for exposure assessment.
- The composition of the e-liquid is representative for the vapor. This means that the e-liquid constituents transfer to the vapor proportionally.
- The vapor will consist of e-liquid constituents only, no substances from other sources, such as the device, will evaporate.
- The ratio of propylene glycol:glycerol in the liquid is 1:1. This ratio is used to calculate the e-liquid weight to a volume (density of the mixture is 1148 mg/ml).

We have used four exposure scenarios, from low to high exposure level:

1. Weekly user: 8 puffs/session, 7 sessions/day, 1 day/week
2. Daily user: 7 puffs/session, 16 sessions/day, 7 days/week
3. Daily user with a higher e-liquid consumption: 8 puffs/session, 16 sessions/day, 7 days/week
4. Daily user with the highest e-liquid consumption: 10 puffs/session, 20 sessions/day, 7 days/week

Scenarios 3 and 4 assume that the users have a higher e-liquid consumption, for example by adapting the device setting to vaporize more e-liquid. These scenarios were selected since the quantity of e-liquid use per puff was measured at a relatively mild scenario, whereas user information from fora indicated a daily e-liquid use of 10 ml/day (as in scenario 4). This means that even the most intense scenario is considered relevant and also higher exposure levels may be realistic. Table S1.1 shows the total e-liquid exposure.

Table S1.1: Exposure to the total volume of e-liquid per day, according to different exposure scenarios.

Scenario	Average quantity of e-liquid per puff	Number of puffs per session	Number of sessions per day	E-liquid consumption per day (in weight)	E-liquid consumption per day (in volume)	Systemic exposure
	mg/puff	number	number	mg/day	ml/day	ml/day
1	12.41	8	7	695	0.61	0.42
2	12.41	7	16	1390	1.21	0.85
3	24.81	8	16	3176	2.77	1.94
4	57.40	10	20	11480	10.00	7.00

The systemic exposure to the total volume of e-liquid per day (Table S1.1) was used to calculate the systemic exposure to each of the flavorings. Results are shown in Table S1.2). The method used for this calculation is described in the materials and methods section of the main text.

For evaluation of health effects, the most intense scenario was assessed first. If a possible health risk was found, further assessments were done for scenarios 3, 2 and finally 1.

Table S1.2: Absorbed dose of the 23 flavorings according to 4 exposure scenarios, for the median and maximum concentration found in e-liquids in the EU common entry gate (EU-CEG).
Bw = body weight

	Daily dose (µg/kg bw/day) median				Daily dose (µg/kg bw/day) maximum			
Substance name	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 1	Scenario 2	Scenario 3	Scenario 4
2,3,5-Trimethylpyrazine	1.00	1.99	4.55	16.46	140.94	281.88	644.30	2328.77
Damascenone	0.16	0.31	0.72	2.60	223.85	447.69	1023.29	3698.63
Isophorone	0.24	0.47	1.08	3.92	167.04	334.07	763.59	2759.96
beta-Damascone	3.27	6.54	14.94	54.00	66.23	132.47	302.79	1094.40
(E)-beta-Damascone	0.85	1.71	3.90	14.09	50.81	101.62	232.26	839.50
(Z)-beta-Damascone	0.63	1.26	2.88	10.40	5.58	11.16	25.50	92.16
Keto-isophorone	0.18	0.36	0.83	3.00	4.34	8.68	19.84	71.73
Tabanone	0.83	1.66	3.79	13.72	35.23	70.47	161.07	582.19
beta-Caryophyllene	0.31	0.63	1.44	5.20	279.44	558.89	1277.46	4617.30
(E)-beta-Damascenone	0.70	1.40	3.20	11.55	25.54	51.08	116.75	422.00
Isovaleric acid	0.01	0.02	0.05	0.18	9.57	19.15	43.77	158.20
2-Hydroxy-3,5,5-trimethyl-2-cyclohexenone	3.15	6.29	14.38	51.98	24.82	49.64	113.46	410.09
Pyridine	0.10	0.21	0.47	1.70	140.94	281.88	644.30	2328.77
3-Acetylpyridine	0.50	1.01	2.30	8.31	2.20	4.40	10.07	36.38
2-Ethyl-3-methylpyrazine	0.04	0.07	0.17	0.60	2.42	4.84	11.07	40.00
2,6-Dimethoxyphenol	0.11	0.22	0.49	1.78	2.79	5.58	12.75	46.10
p-Cresol	0.02	0.04	0.08	0.30	0.85	1.69	3.87	14.00
(-)Carophyllene oxide	0.06	0.11	0.26	0.94	0.31	0.62	1.41	5.10
alpha-Angelica lactone	0.01	0.02	0.04	0.14	0.13	0.27	0.61	2.19
Ambroxide	0.02	0.03	0.07	0.26	1.94	3.87	8.85	31.99

	Daily dose (µg/kg bw/day) median				Daily dose (µg/kg bw/day) maximum			
Substance name	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 1	Scenario 2	Scenario 3	Scenario 4
3-Ethylpyridine	0.00	0.01	0.01	0.05	1.21	2.42	5.53	20.00
5-(Hydroxymethyl)-2-furfural	0.01	0.02	0.06	0.20	0.11	0.21	0.49	1.76
(3aR)-(+)-Sclareolide	0.01	0.01	0.03	0.10	1.51	3.03	6.92	25.00

References

1. Visser W, Geraets L, Klerx W, Hernandez L, Croes E, Schwillens P, Cremers H, Bos P, Talhout R. 2015. De gezondheidsrisico's van het gebruik van e-sigaretten. RIVM-report 2014-0143.