Supplementary file 2: Points of Departure (PoD)

Table S2: Overview of the available toxicological data of the flavorings.

Substance name	Reference	Limit value	Remarks
2,3,5-Trimethylpyrazine	JECFA, 2002[1]	NOAEL: 18 mg/kg bw/day	90-day oral study with rats (diet, 1 dose). No observed effects.
Damascenone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Isophorone	ECHA, 2022a[3] and NTP, 1986[4]	CMR	Harmonised classification Carc. 2 (H351; suspected of causing cancer)
beta-Damascone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
(E)-beta-Damascone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
(Z)-beta-Damascone	EFSA, 2015[2]	TTC 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Ketoisophorone	EFSA, 2015[2]	TTC: 540 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Tabanone	JECFA, 2011[5]	NOAEL: 40 mg/kg bw/day	14-day oral study with rats (gavage, 0, 40, 200 and 1000 mg/kg bw/day). Based on increased liver weight and decreased spleen weight.
Beta-Caryophyllene	ECHA, 2022b[6]	(potentially) sensitizing	Notified classification Skin. Sens. 1B (H317; may cause allergic skin reaction). Based on studies with mice and guinea pigs and a clinical study.
(E)-beta-Damascenone	EFSA, 2015[2]	TTC: 1800 µg/person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.
Isovaleric acid	EFSA, 2012[7]	TTC: 1800 µg/person/day	Evaluated as part of a group of branched-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing branched-chain alcohols and acetals containing branched-chain aldehydes.
2-Hydroxy-3,3,5-trimethyl-2-cyclohexanone	EFSA, 2015[2]	TTC: 540 µg/ person/day	Evaluated as part of a group of α,β-unsaturated alicyclic ketones.

Substance name	Reference	Limit value	Remarks
Pyridine	IARC, 2019[8]	CMR	IARC Classification 2B; possibly carcinogenic to humans.
3-Acetylpyridine	EFSA, 2018[9]	TTC: 540 µg/person/day	Evaluated as part of a group of pyridine, pyrrole and quinoline derivatives.
2-Ethyl-3-methylpyrazine	JECFA, 2002[1]	NOAEL: 5.2 mg/kg bw/day	90-day oral study with rats (diet, 1 dose). No observed effects.
2,6-Dimethoxyphenol	EFSA, 2008[10]	TTC: 1800 µg/person/day	Evaluated as part of a group of phenol derivatives containing ring-alkyl, ring-alkoxy and side-chains with an oxygenated functional group.
p-Cresol	ECHA, 2022c[11]	DNEL of 3.5 mg/m^3 based on an oral NOAEL of 50 mg/kg bw/day	90-day oral study (gavage, 0, 50, 175 or 600 mg/kg bw/day).
(-)-Caryophyllene-oxide	EFSA, 2014[12] and Bauter, 2013[13]	NOAEL: 109 mg/kg bw/day	90-day oral study with rats (diet, 0, 109, 672 and 1398 mg/kg bw/day). Based on mesenteric lymph node pathology.
alpha-Angelica lactone	JECFA, 1998[14]	NOAEL: 17.4 mg/kg/day	90-day oral study with rats (drinking water, highest dose). No observed effects.
Ambroxide	EFSA, 2010[15]	TTC: 90 µg/person/day	Evaluated as part of a group of aliphatic and aromatic ethers.
3-Ethylpyridine	EFSA, 2018[9]	TTC: 540 µg/person/day	Evaluated as part of a group of pyridine, pyrrole and quinoline derivatives.
5-(Hydroxymethyl)-2-furfural	EFSA, 2011[16] derived from NTP, 2010[17]	BMDL: 14.4 mg/kg bw/day	90-day oral study with mice (gavage, 0, 47, 94, 188, 375 or 750 mg/kg). Corrected for dose regimen of 5 days/week to continuous daily administration). Based on cytoplasmic alterations in renal proximal tubule epithelium.
(3aR)-(+)-Sclareolide	EFSA, 2014[12]	TTC: 90 µg/person/day	Evaluated as part of a group of epoxides.

Abbreviations

BMDL: benchmark dose level
CLP: Classification, Labelling and Packaging
CMR: Carcinogenic, Mutagenic, Reprotoxic
DNEL: derived no effect level
ECHA: European Chemicals Agency
EFSA: European Food Safety Authority
IARC: International Agency for Research on Cancer
JECFA: Joint FAO/WHO Expert Committee on Food Additives
NOAEL: no-observed adverse effect level
NTP: National Toxicology Program
TTC: threshold of toxicological concern

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