Supplementary file 2: Points of Departure (PoD)

Table S2: Overview o	t the available toxic	cological data of the	flavorings.
Substance name	Reference	Limit value	Remarks
2,3,5-	JECFA, 2002[1]	NOAEL: 18 mg/kg	90-day oral study with rats
Trimethylpyrazine		bw/day	(diet, 1 dose). No observed
			effects.
Damascenone	EFSA, 2015[2]	TTC 1800	Evaluated as part of a
Dumuseemone	21 511, 2010[2]	ug/person/day	group of a B-unsaturated
		µg/person/duy	alicyclic ketones
Isophorona	ECHA 20220[2]	CMP	Hermonicad elegification
isophotolie	ECHA, 2022a[5]	CIVIK	Game 2 (11251), successful
	and NTP, 1980[4]		Carc. 2 (H351; suspected
			of causing cancer)
beta-Damascone	EFSA, 2015[2]	TTC 1800	Evaluated as part of a
		µg/person/day	group of α , β -unsaturated
			alicyclic ketones.
(E)-beta-Damascone	EFSA, 2015[2]	TTC 1800	Evaluated as part of a
		µg/person/day	group of α , β -unsaturated
			alicyclic ketones.
(Z)-beta-Damascone	EFSA, 2015[2]	TTC 1800	Evaluated as part of a
		µg/person/day	group of α,β -unsaturated
			alicyclic ketones.
Ketoisophorone	EFSA, 2015[2]	TTC: 540	Evaluated as part of a
	. ,	ug/person/day	group of α β -unsaturated
		µB, person, aug	alicyclic ketones
Tabanone	IECEA 2011[5]	NOAFL · 40 mg/kg	14-day oral study with rate
rubunone	JECI II, 2011[5]	hw/day	(gauage 0, 40, 200 and
		0w/uay	(gavage, 0, 40, 200 and 1000 mg/kg hu/day)
			1000 liig/kg bw/day).
			Based on increased liver
			weight and decreased
			spleen weight.
Beta-Caryophyllene	ECHA, 2022b[6]	(potentially)	Notified classification
		sensitizing	Skin. Sens. 1B (H317; may
			cause allergic skin
			reaction). Based on studies
			with mice and guinea pigs
			and a clinical study.
(E)-beta-	EFSA, 2015[2]	TTC: 1800	Evaluated as part of a
Damascenone		µg/person/day	group of α,β -unsaturated
			alicyclic ketones.
Isovaleric acid	EFSA, 2012[7]	TTC: 1800	Evaluated as part of a
	,	ug/person/day	group of branched-chain
		P.8. F	primary aliphatic
			alcohols/aldehydes/acids
			acetals and esters with
			esters containing branched
			chain alcohols and sectors
			chain alcohols and acetals
			-1d-haining oranched-chain
211 1 225			aldenydes.
2-Hydroxy-3,3,5-	EFSA, 2015[2]	TTC: 540 μg/	Evaluated as part of a
trimethyl-2-		person/day	group of α,β -unsaturated
cyclohexanone	1	1	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	Evaluated as part of a
		µg/person/day	group of pyridine, pyrrole
			and quinoline derivatives.
2-Ethyl-3-	JECFA, 2002[1]	NOAEL: 5.2 mg/kg	90-day oral study with rats
methylpyrazine		bw/day	(diet, 1 dose). No observed
2.6-Dimethoxyphenol	EESA 2008[10]	TTC: 1800	Evaluated as part of a
2,0-Dimetioxypitenoi	LI 5A, 2000[10]	ug/person/day	group of phenol
		µg/person/day	derivatives containing
			ring-alkyl, ring-alkoxy and
			side-chains with an
			oxygenated functional
			group.
p-Cresol	ECHA, 2022c[11]	DNEL of 3.5	90-day oral study (gavage,
		mg/m ³ based on an	0, 50, 175 or 600 mg/kg
		oral NOAEL of 50	bw/day).
		mg/kg bw/day	
(-)-Caryophyllene-	EFSA, 2014[12]	NOAEL: 109	90-day oral study with rats
oxide	and Bauter,	mg/kg bw/day	(diet, 0, 109, 672 and 1398
	2013[13]		mg/kg bw/day). Based on
			mesenteric lymph node
1.1. A. 1.	IECEA 1000[14]	NOAFI 174	pathology.
alpha-Angelica	JECFA, 1998[14]	NOAEL: 17.4	90-day oral study with rats
lactone		mg/kg/day	(drinking water, nignest
			uose). No observed effects.
Ambroxide	EFSA, 2010[15]	TTC: 90	Evaluated as part of a
	, , , , , , , , , , , , , , , , , , , ,	µg/person/day	group of aliphatic and
			aromatic ethers.
3-Ethylpyridine	EFSA, 2018[9]	TTC: 540	Evaluated as part of a
		µg/person/day	group of pyridine, pyrrole
			and quinoline derivatives.
5-(Hydroxymethyl)-	EFSA, 2011[16]	BMDL: 14.4 mg/kg	90-day oral study with
2-furfural	derived from	bw/day	mice (gavage, 0, 47, 94,
	NTP, 2010[17]		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
$(2n\mathbf{D})$ (1) Salaman \mathbf{b}^{\dagger}	EESA 2014[12]	TTC: 00	Evoluated as most of a
(Jak)-(+)-Sciareolide	EFSA, 2014[12]	11C:90	Evaluated as part of a
		µg/person/day	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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