

# ASPARTAME, METHYLEUGENOL, AND ISOEUGENOL

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ON THE IDENTIFICATION  
OF CARCINOGENIC HAZARDS  
TO HUMANS

# LIST OF ABBREVIATIONS

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acesulfame-K	acesulfame potassium
ADI	acceptable daily intake
AhR	aryl hydrocarbon receptor
AHRR	aryl hydrocarbon receptor repressor
AIF	apoptosis-inducing factor
ANOVA	analysis of variance
APF	aminophenyl fluorescein
AR	androgen receptor
ASB	artificially sweetened beverage
ATP	adenosine triphosphate
AUC	area under the curve
BBN	<i>N</i> -butyl- <i>N</i> -(4-hydroxybutyl)nitrosamine
BMI	body mass index
BUN	blood urea nitrogen
bw	body weight
CAM	chorioallantoic membrane
cAMP	cyclic adenosine monophosphate
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CAT	catalase
CDK	cyclin-dependent kinase
CI	confidence interval
CLL	chronic lymphocytic leukaemia
$C_{\max}$	maximum concentration
CPID	Consumer Product Information Database
CPS	Cancer Prevention Study
CPS-II	Cancer Prevention Study II
CRP	C-reactive protein
CYP	cytochrome P450
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1
DAG	directed acyclic graph
DCFDA	2',7'-dichlorodifluorescein diacetate

DKP	diketopiperazine
DPPH	1,1-diphenyl-2-picrylhydrazyl
DRIFTS	diffuse reflectance infrared Fourier transform spectroscopy
DSPE	dispersive solid-phase extraction
dw	dry weight
EC <sub>50</sub>	half-maximal effective concentration
EFSA	European Food Safety Authority
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMT	epithelial–mesenchymal transition
EPIC	European Prospective Investigation into Cancer and Nutrition
ERE	estrogen receptor binding element
ERK	extracellular signal-regulated kinase
FAO	Food and Agriculture Organization of the United Nations
FFQ	food frequency questionnaire
FLD	fluorescence detection
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GABA <sub>A</sub> receptor	gamma-aminobutyric acid type A receptor
GC	gas chromatography
GCG	proglucagon
GC-MS	gas chromatography-mass spectrometry
GC-MS/MS	gas chromatography-tandem mass spectrometry
GLI1	GLI family zinc finger 1
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
GLP-2R	glucagon-like peptide-2 receptor
GMVEC	glomerular microvascular endothelial cells
GPx	glutathione peroxidase
GR	glucocorticoid receptor
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRAS	generally recognized as safe
GSH	glutathione
GSR	glutathione reductase
GSSG	glutathione disulfide
GST	glutathione S-transferase
GTT	glucose tolerance test
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HFS	high-fat/sucrose
HIV	human immunodeficiency virus
HOMA-B	homeostatic model assessment for insulin secretion
HOMA-IR	homeostatic model assessment for insulin resistance
HPFS	Health Professionals Follow-up Study
HPLC	high-performance liquid chromatography
HPLC-UV	high-performance liquid chromatography-ultraviolet detection
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein

HS-PTV-fast GC-MS	headspace-programmed temperature vapourization-fast gas chromatography-quadrupole mass spectrometry
HS-SPME	headspace solid-phase microextraction
hTRPA1	human transient receptor potential ankyrin 1
HUVEC	human umbilical vein endothelial cells
IARC	International Agency for Research on Cancer
IC <sub>50</sub>	half-maximal inhibitory concentration
ICAM-1	intracellular adhesion molecule 1
IFN $\gamma$	interferon gamma
Ig	immunoglobulin
IGF-1	insulin-like growth factor 1
IGF-1R	insulin-like growth factor 1 receptor
IL	interleukin
iNOS	inducible isoform of nitric oxide synthase
ISO	International Organization for Standardization
ITT	insulin tolerance test
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC	liquid chromatography
LC-ELSD	liquid chromatography-evaporative light-scattering detection
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LH	luteinizing hormone
LIRI	liver ischaemia reperfusion injury
LLN	local lymph node
LLNA	local lymph node assay
LOD	limit of detection
LOQ	limit of quantification
LOOH	lipid hydroperoxides
Lp-PLA2	lipoprotein-associated phospholipase A2
LTC <sub>4</sub>	leukotriene C <sub>4</sub>
LTT	lymphocyte transformation test
MAPK	mitogen-activated protein kinase
MCCS	Melbourne Collaborative Cohort Study
MCC-Spain	Spanish Multicase-Control Study
MDA	malondialdehyde
MDCK	Madin-Darby canine kidney
N <sup>2</sup> -MIE-dG	N <sup>2</sup> -(methylisoeugenol-3'-yl)-2'-deoxyguanosine
N <sup>6</sup> -MIE-dA	N <sup>6</sup> -(methylisoeugenol-3'-yl)-2'-deoxyadenosine
MoLC	monocyte-derived LC-like cells
MRL	maximum residue level
MS	mass spectrometry
MSG	monosodium glutamate
MSDI	maximized survey-derived daily intake
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NAC	N-acetyl cysteine
ND	not detected
NF- $\kappa$ B	nuclear factor kappa-light-chain-enhancer of activated B-cells
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
NHS	Nurses' Health Study

NHS-II	Nurses' Health Study II
NIH-AARP	National Institutes of Health-American Association of Retired Persons Diet and Health Study
NIOSH	National Institute for Occupational Safety and Health
NICD	notch intracellular domain
NLRP3	NLR family pyrin domain containing 3
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
NMDAR	<i>N</i> -methyl- <i>D</i> -aspartate receptor
NMR	nuclear magnetic resonance
NO	nitric oxide
NOES	National Occupational Exposure Survey
NPSH	non-protein thiol
NR	not reported
NTP	National Toxicology Program
OCT	octameric transcription factor
OECD	Organisation for Economic Co-operation and Development
OGTT	oral glucose tolerance test
OR	odds ratio
oxLDL	oxidized low-density lipoprotein
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
Phe/LNAA	phenylalanine/large neutral amino acids
PKU	phenylketonuria
PLCO	Prostate, Lung, Colorectal and Ovarian
PLE	pressurized liquid extraction
PMRA	Pest Management Regulatory Agency
PPAR	peroxisome proliferator-activated receptor
PPAR $\gamma$	peroxisome proliferator-activated receptor gamma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PXR	pregnane X receptor
qRT-PCR	quantitative reverse transcription-polymerase chain reaction
RHS	reconstructed human skin
ROS	reactive oxygen species
RR	relative risk
RT-PCR	reverse transcription-polymerase chain reaction
SCE	sister-chromatid exchange
SD	Sprague-Dawley
SFE	supercritical fluid extraction
SGOT	serum glutamic-oxaloacetic transaminase (aspartate aminotransaminase)
SGPT	serum glutamic pyruvic transaminase (alanine aminotransaminase)
sHR	subdistribution hazard ratio
sIL-6r	soluble interleukin-6 receptor
SIM-GC-MS	selected ion monitoring-gas chromatography-mass spectrometry
siRNA	small interfering RNA
SMART	somatic mutation and recombination by wing spot test
SOD	superoxide dismutase
SPE	solid-phase extraction
SREBP	sterol regulatory element-binding protein
SV40	simian virus 40
T3	triiodothyronine
T4	thyroxine

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TAC	total antioxidant capacity
TBARS	thiobarbituric acid reactive substances
TIR	sweet taste receptor 1
$T_{\max}$	the time taken to reach maximum concentration
TNF $\alpha$	tumour necrosis factor alpha
TOS	total antioxidant status
TRAP	thrombin receptor-activating protein
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labelling
UAE	ultrasound-assisted solvent extraction
UDS	unscheduled DNA synthesis
UK	United Kingdom
UPLC	ultra-performance liquid chromatography
UPLC-MS/MS	ultraperformance liquid chromatography-tandem mass spectrometry
US	United States
USA	United States of America
US FDA	United States Food and Drug Administration
UV	ultraviolet
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WWTP	wastewater treatment plant
XO	xanthine oxidase