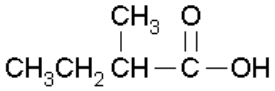
Methyl butyric acid, 2-

Ingredient synonym names

Butanoic acid, 2-methyl- (9CI)
Butyric acid, 2-methyl- (8CI)
Active valeric acid
Butane-2-carboxylic acid
Butyric acid, 2-methyl-(6ci,8ci)
Ethylmethylacetic acid
2-Methybutyric acid
2-Methylbutanoic acid
2-Methylbutyric acid (VAN)
Methylethylacetic acid

IDENTIFIER DETAILS

Ingredient chemical structure



CAS Number	FEMA Number	Additive Number	Ingredient EC Number
116-53-0	2695	-	204-145-2

CAS Additional Number	FL Number	CoE Number
600-07-7	08.046	2002

Chemical formula C5H10O2

Ingredient CLP Classification

Ingredient REACH Registration Number

01-2119959862-23

Acute Oral Toxicity	Eye Damage/Irritation	Carcinogenity
4	1	0

Acute Dermal Toxicity	Respiratory Sensitisation	Reproductive Toxicity
4	0	0

Acute Inhalation Toxicity	Skin Sensitisation	Aspiration Toxicity
0	0	0

Skin Corrosive/Irritant	Mutagenicity/ Genotoxicity	Specific Target Organ Toxicity
1B	0	0

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SPECIFICATIONS

Melting Point	NA	Boiling Point	176-177oC

STATUS IN FOOD AND DRUG LAWS

Acceptable Daily Intake (ADI, mg/kg)	ACCEPTABLE
Acceptable Daily Intake (ADI) comments	No safety concern at current levels of intake when used as a flavouring agent.
FDA Status	[CFR21] 172.515 Synthetic flavouring substances and adjuvants for the addition to foo for human consumption

CoE limits - Beverages (mg/kg)	0.5	CoE limits - Food (mg/kg)	15	CoE limits - Exceptions (mg/kg)	-

HUMAN EXPOSURE

Ingredient Natural Occurence (if applicable)

As the d-, l- and dl-isomers the racemic form has been reportedly found in angelica root oil and coffee and the d-isomer in the ester form has been identified in lavender oil. Also reportedly found in apple, apricot, berries, grapes, tomato, beer, rum, tea, peppermint, spearmint oil and Roman chamomile oil [Fenaroil, 2005].

References - Ingredient Natural Occurence

Fenaroli (2005). Fenaroli's handbook of flavour ingredients, 5th Edition CRC press.

Ingredient Reported Uses

Methyl butyric acid is reportedly used in baked goods at 17.5ppm, frozen dairy at 8.62ppm, cheese 50ppm, soft candy at 6.05ppm, gelatin pudding at 5.92ppm, non-alcoholic beverages at 1.04ppm, and alcoholic beverages at 3ppm. Individual consumption has been reported to be 0.007711mg/kg/day [Fenaroli, 2005].

References - Ingredient Reported Uses

Fenaroli (2005). Fenaroli's handbook of flavour ingredients, 5th Edition CRC press.

TOXICITY DATA

In Vivo Data

Acute Toxicity Data

1870 ul/kg Rat Oral
1460 ul/kg Rabbit Skin
[RTECS, 2003]

RTECS (2003). CIS Record ID RTEC-0038742 obtained from http://biblioline.nisc.com

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In Vivo Carcinogenicity/Mutagenicity

No data identified.

References - In Vivo Carcinogenicity/Mutagenicity

No data identified.

Dermal Toxicity

No data identified.

References - Dermal Toxicity

No data identified.

Reproductive/ Developmental Toxicity

No data identified.

References - Reproductive/ Developmental Toxicity

No data identified.

Inhalation Toxicity

No data identified.

References - Inhalation Toxicity

No data identified.

Cardiac Toxicity

No data identified.

References - Cardiac Toxicity

No data identified.

Addictive Data

No data identified.

References - Addictive Data

No data identified.

Behavioral data

No data identified.

References - Behavioral data

No data identified.

In Vivo - Other Relevant Studies

No data identified.

References - In Vivo - Other Relevant Studies

No data identified.

In Vitro Data

In Vitro Carcinogenicity/Mutagenicity

No data identified.

References - In Vitro Carcinogenicity/Mutagenicity

No data identified.

In Vitro - Other Relevant Studies

It has been reported that, branched-chain aliphatic acyclic alcohols, aldehydes and acids are rapidly absorbed from the gastrointestinal tract, [JECFA, 1998]. Branched-chain acids are reported to be metabolized via ß-oxidation in the longer branched-chain. This is then followed by cleavage to yield linear acid fragments, which are completely metabolized in the fatty acid pathway or the tricarboxylic acid cycle. At high concentrations, longer branched-chain acids are reported to undergo omega-oxidation to yield diacids, which may undergo further oxidation and cleavage [JECFA, 1998].

The Expert Panel for Fragrance Safety concludes that this material is safe as described in this safety assessment. 2-Methylbutyric acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on the target material and read-across analog isobutyric acid (CAS # 79-31-2) show that 2-methylbutyric acid is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2-methylbutyric acid is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 µg/cm2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-methylbutyric acid is not expected to be phototoxic/photoallergenic [Api, et al., 2019].

References - In Vitro - Other Relevant Studies

JECFA (1998). Safety evaluation of certain food additives and contaminants. Prepared by the forty-ninth meeting of the joint FAO/WHO Expert Committee on Food Additives (JECFA). ICPCS Geneva.

A.M. Api, F. Belmonte, D. Belsito, D. Botelho, M. Bruze, G.A. Burton, J. Buschmann, M.L. Dagli, M. Date, W. Dekant, C. Deodhar, A.D. Fryer, S. Gadhia, L. Jones, K. Joshi, S. La Cava, A. Lapczynski, M. Lavelle, D.C. Liebler, M. Na, D. O'Brien, T.M. Penning, G. Ritacco, J. Romine, N. Sadekar, D. Salvito, T.W. Schultz, I.G. Sipes, G. Sullivan, Y. Thakkar, Y. Tokura, S. Tsang (2019). RIFM fragrance ingredient safety assessment, 2-methylbutyric acid, CAS Registry Number 116-53-0, Food and Chemical Toxicology, Volume 130, Supplement 1

Emissions and Associated Toxicity Data

Carmines (2002), Rustemeier et al., (2002), Roemer et al., (2002) and Vanscheeuwijck et al., (2002) reported on a testing program designed to evaluate the potential effects of 333 ingredients added to typical commercial blended

test cigarettes on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the addition of the combined ingredients, including methyl butyric acid at levels up to 5 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines (2002), Rustemeier et al., (2002), Roemer et al., (2002) and Vanscheeuwijck et al., (2002)].

Renne et al., (2006) evaluated the effects of tobacco flavouring and casing ingredients on both mutagenicity, and a number of physiological parameters in Sprague-Dawley (SD) rats. Test cigarettes containing a mixture of either 165 low-uses or eight high-use flavouring ingredients which included methyl butyric acid at 0.65ppm, were compared to a typical commercial tobacco blend without flavouring ingredients. The Ames assay (TA 98, 100,102, 1535 and 1537 ±S9) did not show any increase in Mutagenicity from "low" or "high" cigarette smoke condensate compared to the control. SD rats were exposed by nose-only inhalation for 1h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8mg/L from the test or reference cigarettes, or to air only. Plasma nicotine, COHb and respiratory parameters were measured periodically. Rats were necropsied after 13wk of exposure or following 13 wk of recovery from smoke exposure. Biological endpoints assessed included; clinical appearance, body weight, organ weights, and lesions (both gross and microscopic). The results of these studies did not indicate any consistent differences in toxicological effects between smoke from cigarettes containing the flavouring or casing ingredients and reference cigarettes.

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including Methylbutyric acid at levels up to 108 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

A recent mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including methyl butyric acid at 0.4 ppm. The authors concluded that the study "did not indicate any substantive effect of these ingredients on the tumorigenicity of cigarette smoke condensate" [Gaworski et al., 1999]. [It should be noted that the cigarettes contained a typical American blend humectant and sugar component (i.e. glycerine □ 20,000 ppm, propylene glycol at □ 24,000 ppm, and brown invert sugar at □ 24,000 ppm)] [Gaworski et al., 1999].

The addition of methyl butyric acid at 12 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of methyl butyric acid to a reference cigarette had no discernable effect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker et al., 2004].

A recent study investigated the effect of cigarettes, containing various additives in three combinations, in a 90-day nose-only smoke inhalation study in rats. These ingredients included methyl butyric acid at 5ppm, a level described as a multiple of its typical use in a US cigarette. The data from this study along with that from a number of other biological and chemical studies indicate that the addition of the combined ingredients "did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used" [Vanscheeuwijck et al., 2002].

When tested at 0.4 ppm in cigarettes, in a 13-week inhalation study, the presence of methyl butyric acid "…had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats."[Gaworski et al., 1998]. [However, it should be noted that the cigarettes had been spiked with a number of flavour ingredients in combination prior to smoking, and they contained a typical American blend humectant and sugar component (i.e. glycerine □ 20,000 ppm, propylene glycol at □ 24,000 ppm,

and brown invert sugar at □ 24,000 ppm)] [Gaworski et al., 1998].

The mutagenicity of the smoke condensate was assayed in the Salmonella plate incorporation [Ames] assay with the tester strain TA98 in the presence of an S9 metabolic activation system. The cytotoxicity of the cigarette condensate was determined in the neutral red uptake assay and the (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt assay (MTS assay) with the human hepatocellular liver carcinoma cell line, HEP-G2. It was concluded that the in vitro mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included methyl butyric acid at levels up to 16 ppm.

Additional information concerning the in vitro mutagenicity of this material may be found in "An Interim report on data originating from Imperial Tobacco Limited's Genotoxicity testing programme September 2003" or "An updated report on data originating from Imperial Tobacco Limited's external Genotoxicity testing programme – Round 2 August 2007".

References - Emissions and Associated Toxicity Data

Baker RR, et al., (2004). An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. Food & Chemical Toxicology. 42 Suppl: S53-83.

Carmines (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 1: Cigarette design, testing approach, and review of results. Food & Chemical Toxicology 40: 77-91.

Gaworski et al., (1998). Toxicologic evaluation of flavour ingredients added to cigarette tobacco: 13-week inhalation exposure in rats. Inhalation Toxicology. 10: 357-381.

Gaworski et al., (1999). Toxicologic evaluation of flavour ingredients added to cigarette tobacco: skin painting bioassay of cigarette smoke condensate in SENCAR mice. Toxicology 139: 1-17.

Renne et al., (2006). Effects of flavouring and casing ingredients on the toxicity of mainstream cigarette smoke in rats. Inhalation Toxicology. 18:685-706.

Roemer (2014) Toxicological assessment of kretek cigarettes: Part 1: background, assessment approach, and summary of findings. Regul Toxicol Pharmacol.; 70 Suppl 1: 2-14.

Roemer (2014) Toxicological assessment of kretek cigarettes Part 6: the impact of ingredients added to kretek cigarettes on smoke chemistry and in vitro toxicity. Regul Toxicol Pharmacol.; 70 Suppl 1: 66-80.

Roemer et al., (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 3: In vitro genotoxicity and cytotoxicity. Food & Chemical Toxicology 40: 105-111.

Rustemeier et al., (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 2: Chemical composition of mainstream smoke. Food & Chemical Toxicology 40: 93-104.

Schramke (2014) Toxicological assessment of kretek cigarettes. Part 7: the impact of ingredients added to kretek cigarettes on inhalation toxicity. Regul Toxicol Pharmacol; 70 Suppl 1: 81-9.

Vanscheeuwijck et al., (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 4: Subchronic inhalation toxicity. Food & Chemical Toxicology 40: 113-131.

In vitro toxicity testing of e-liquid ingredients in vapour generated by an EVP
(Internal document Report: IVM 01; Report: AMES 02)

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