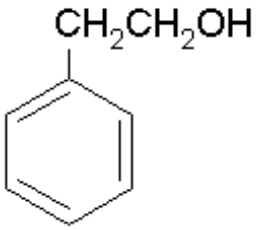
Phenethyl alcohol

Ingredient synonym names

1-Phenyl-2-ethanol
2-Phenyl ethanol
2-Phenyl ethyl alcohol
Benzyl carbinol
Benzyl methanol
Beta-hydroxy ethyl benzene
Beta-PEA.
Beta-phenyl ethyl alcohol
Phenethylol
Phenyl ethyl alcohol

IDENTIFIER DETAILS

Ingredient chemical structure



CAS Number	FEMA Number	Additive Number	Ingredient EC Number
60-12-8	2858	-	200-456-2

CAS Additional Number	FL Number	CoE Number
-	02.019	68

Chemical formula C8H10O

Ingredient CLP Classification

Ingredient REACH Registration Number

1-2119963921-31

Acute Oral Toxicity	Eye Damage/Irritation	Carcinogenity
4	2	0
Acute Dermal Toxicity	**Respiratory Sensitisation**	**Reproductive Toxicity**
0	0	0
Acute Inhalation Toxicity	**Skin Sensitisation**	**Aspiration Toxicity**
0	0	0
Skin Corrosive/Irritant	**Mutagenicity/ Genotoxicity**	**Specific Target Organ Toxicity**
0	0	0

Phenethyl alcohol

SPECIFICATIONS

Melting Point	-27°C	Boiling Point	219-221°C at 740 mmHg

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 - JECFA (2002)
FDA Status	172.515: Synthetic flavouring substances and adjuvants

CoE limits - Beverages (mg/kg)	2	CoE limits - Food (mg/kg)	20	CoE limits - Exceptions (mg/kg)	-

HUMAN EXPOSURE

Ingredient Natural Occurence (if applicable)

Phenethyl alcohol is reported to be found [as is or esterified] in several natural products: rose concrete, rose absolute (60% or more), and rose distillation waters; also found in the essential oils of neroli, ylang ylang, narcissus, hyacinth, lily, tea leaves, Michelia champaca, Pandamus odorastissimus, Congo and Reunion geranium, tobacco, and others; it has been identified in wines. It occurs widely; in over 200 foods and beverages including apple, melon, milk, soybean, mango and watercress [Fenaroli, 2005].

References - Ingredient Natural Occurence

Fenaroli (2005). Fenaroli's Handbook of Flavour Ingredients, 5th Edition. CRC Press, Boca Raton, USA.

Ingredient Reported Uses

Phenethyl alcohol is reportedly used in baked goods at 32.84 ppm, fats, oils at 0.1 ppm, frozen dairy at 23.37 ppm, soft candy at 30.01 ppm, gelatin, pudding at 9.87 ppm, non-alcoholic beverages at 17.84 ppm, alcoholic beverages at 6.60 ppm, hard candy at 2.45 ppm, and chewing gum at 78.78 ppm [Fenaroli, 2005].

References - Ingredient Reported Uses

Fenaroli (2005). Fenaroli's Handbook of Flavour Ingredients, 5th Edition. CRC Press, Boca Raton, USA.

TOXICITY DATA

In Vivo Data

Acute Toxicity Data

Acute toxicity Lethal Dose (taken from Scognamiglio et al., 2012)

Route	Species	Animals/dose group	LD50(g/kg)
Oral	Mouse	Not reported	0.8-1.5

Phenethyl alcohol

Oral	Rat	4	1.6
Oral	Rat	10	1.79
Oral	Rat	Not reported	0.65 (f) 1.43 (m)
Oral	Rat	Not reported	1.8
Oral	Rat	10	1.5
Oral	Rat	Not reported	2.19
Oral	Rat	Not reported	1.79
Oral	Rat	Not reported	2.46
Oral	Guinea pig	Not reported	2.54
Oral	Guinea pig	Not reported	0.4-0.8
Dermal	Guinea pig	Not reported	5-10
Dermal	Rabbit	8	2.54
Dermal	Rabbit	Not reported	0.79
Dermal	Rabbit	10	>5
Intraperitoneal	Mouse	Not reported	0.2-0.4
Intraperitoneal	Rat	10	0.55
Intraperitoneal	Guinea pig	Not reported	0.4-0.8

Reference

Scognamiglio J, Jones L, Letizia CS, and Api AM (2011). Fragrance material review on phenylethyl alcohol. Food Chem Toxicol. Oct 19. [Epub ahead of print].

Another set of LD50 toxicity data

Species	Test Type	Route	Reported Dosage
Rat	LD50	Oral	1790mg/kg [Lewis, 2000]
Rat	LD50	Oral	3.1ml/kg [Lewis, 2000]
Mouse	LD50	Oral	0.8-1.5g/kg [HSDB, 2002]
Guinea Pig	LD50	Oral	0.4-0.8g/kg [HSDB, 2002]
Guinea Pig	LD50	Intraperitoneal	0.2-0.4g/kg [HSDB, 2002]
Rabbit	LD50	Dermal	790mg/kg [Lewis, 2000]
Rat	LC50	Inhalation	>500mg/m3 [Lewis, 2000]
Rabbit	LD50	Dermal	0.8g/kg [Lewis, 2000]
Guinea Pig	LD50	Dermal	5g/kg [Lewis, 2000]
Mouse	LD50	Subcutaneous	1640mg/kg [Lewis, 2000]
Rabbit	LD50	Oral	2g/kg [Lewis, 2000]
Rat	TDLO	Oral	430mg/kg [Lewis, 2000]
Rat	TDLO	Oral	43mg/kg [Lewis, 2000]

Reference

Brandt (1990). Final report on the safety assessment of phenethyl alcohol, 1990. Journal of the American College of Toxicology. 9(2): 165-83.
HSDB (2002). Hazardous Substances Data Bank found at
Lewis (2000). SAX'S Dangerous Properties of Industrial Materials. 10th Edition. Wiley-Interscience publication. John Wiley and Sons, inc.

In Vivo Carcinogenicity/Mutagenicity

Phenylethyl alcohol was one of the substances reviewed by the Interagency Committee for Chemical Evaluation and Coordination [ICCEC] nominated to the National Toxicology Program. They recommended that no studies be

performed on phenylethyl alcohol as there was no suspicion for carcinogenicity, based on structure and genetic toxicity tests, [National Institute of Environmental Health Sciences National Toxicology Program, 1998].

References - In Vivo Carcinogenicity/Mutagenicity

National Institute of Environmental Health Sciences National Toxicology Program. Request for comments on chemicals nominated to the NationalToxicology Program (NTP) for toxicology studies - recommendations by the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) forstudy, no studies, or deferral to obtain additional information.

Dermal Toxicity

Phenethyl alcohol was observed to be moderately irritating to the skin of rabbits and guinea-pigs [0.1g], whilst observed to be non-irritating to the skin of miniature swine [0.05g] it was also reported not to be a sensitizer for guinea-pig skin at concentrations of 1-2% [Brandt, 1990].

Species	Dosage	Route	Effect
Rabbit	100mg/24H	Skin	Moderate irritant
Guinea pig	100%	Skin	Mild irritant
Guinea pig	100mg /24H	Skin	Moderate
Rabbit	12mg /10M	Eye	Mild irritant
Rabbit	750□g /24H	Eye	Severe irritant

[RTECS, Beilstein reference number 190573]

Dosage	TestGroup	Size	Conclusion
3g/kg bw	Dermal application	2	1 animal sacrificed after 7 days, others survived the full 28 day treatment.
Undiluted	Covered 24 hr/ day for 10 days.	35 female rats	Day 6 signs of irritancy, 1 rat showed blood in urine and inability to walk.
Undiluted			two died day 7. Liver, kidney weight unchanged on autopsy.
0.44g/kg bw/day.	Covered 24 hr/ day for 10 days.	25 female	1 animal showed signs of hunching and walking on toes.
Undiluted 0.14g/kg bw/day.	As above	35 rats	No effects [no microscopic evaluations carried out].
0.25, 0.50, 1.0, and 2.1g /kg bw	90 days on shaved skin [Uncovered].	30 rats	Body weight gain reduced in dose related manner. Increased weight of brain, kidney & gonads for both sexes. The authors regarded 0.25g and 0.5g as NOEL. However, it is thought that there was insufficient liver weight data to independently verify this.

[Taken from BIBRA, 1988]

Phenethyl alcohol

Human Dermal toxicitiy

Dosage	Test	Group Size	Conclusion
Undiluted	24 h [Covered]	20	No irritant effect
32 % in acetone	48 h [Covered]	50	No irritant effect
25 % in petrolatum	48 or 72 h	179	No irritant effect
0.05-0.5 % in cream base or 99 % alcohol	Repeated application 24-48 h [covered]	82	1 subject reported slight redness

[BIBRA, 1988]

A study in which 25 volunteers were involved in a maximisation test [repeated application of 8% Phenethyl alcohol] revealed no evidence of sensitisation [BIBRA, 1988]. A similar study with an eye make up remover containing 0.05% Phenethyl alcohol indicated that it was ‘not a clinically significant irritant or sensitizer’ [Brandt, 1990].

The results of a repeated insult patch test in which 108 subjects were exposed to 8% phenethyl alcohol in diethyl phthalate indicated that two subjects had an irritant response. No other subjects reported irritation or sensitisation [Brandt, 1990].

Bagley et al., (1995) reported phenethyl alcohol to have a primary irritation index of 0.92 and 2.22 on two separate occasions using 3 and 4 rabbits respectively (the maximum possible primary irritation index was 8) [Brandt, 1990]. Phenethyl alcohol at concentrations of 0.02-0.033 % was also observed to have an anaesthetic effect on intradermal injection into wheals on the forearm of three human volunteers [Brandt, 1990].

Members of the Research Institute for Fragrance Materials recently reviewed the available toxicology and exposure data for phenethyl alcohol [Scognamiglio et al., 2012] and more broadly the aryl alkyl alcohols group of materials (including phenethyl alcohol) [Belsito et al., 2012]. The following figures are extracts from Scognamiglio et al., (2012) summarizing the available data. Further information on the individual studies can be found within the text of the article itself.

Figure 3: extract from Scognamiglio et al., (2012). Summary table of human irritation studies:

Method	Dose %	Vehicle	Results Reactions Incidence (%)
HRIPT	8	DEP	0/103 0
HRIPT	2	Alcohol SD-39C	52/93 55.9
HRIPT	25	Ethanol	3/50 6
HRIPT	25	Ethanol	0/39 0

Occluded patch test	0.4%, 2.0% and 20%	Not specified	0/82 at 0.4%, 0/30 at 2% 1/47 at 20%	0.21
Occluded patch test	32%	Acetone	0/50	0
Occluded patch test	100%	N/A	0/20	0
Occluded patch test	0.05%-0.5%	Cream base or 99%	1/82	1.2

Figure 4: extract from Scognamiglio et al., (2012). Summary table of diagnostic patch test studies:

Method	Concentration	Results	
Reactions	Frequency		
Diagnostic patch test	25%	1/179	0.5%
Diagnostic patch test	1%	0/100	0
Diagnostic patch test	5%	0.56	0
Diagnostic patch test	5%	2/20	10%
Aluminium patch test	n/a	0/1	0

Scognamiglio et al., (2012)

Figure 5: extract from Scognamiglio et al., (2012). Summary table of animal irritation studies:

Method	Dose	Species	Reactions
Occluded patch test	100	Guinea pig	Moderately irritating
Occluded patch test	100	Miniature Swine	Non-irritating
Occluded patch test	100	Rabbit	Moderately irritating
Occluded patch test	100	Rabbit	Very slight erythema with one animal showing a slight edematous
Occluded patch test	100	Rabbit	Very slight edema in 2/4 animals,
			well defined erythema and very slight edema.
Occluded patch test	100	Rabbit	Severity increased with exposure duration, with all sites
			returning to normal day 4-5.
Occluded patch test	100	Guinea pig	No irritation.

Acute Derm Toxicity	100	Rabbit	Grade 1 erythema.

Scognamiglio et al., (2012)

Figure 6: extract from Scognamiglio et al., (2012). Summary table of skin sensitization studies:

Method	Concentration	Results Reactions Incidence (%)
HRIPT	8% (9448 microg/cm2)	
2/108	1.9	
HRIPT	25% (12,500 microg/cm2)	
3/89	3.4	
HRIPT	25% (12,500microg/cm2)	
1/50	2	
HRIPT	25% (19380microg/cm2)	
0/39	0	
Maximization	8% (5520 microg/cm2)	
0/25	0	

Scognamiglio et al., (2012)

References - Dermal Toxicity

BIBRA (1988). Phenylethyl alcohol. TNO BIBRA Toxicity profile.

Brandt (1990). Final report on the safety assessment of phenethyl alcohol, 1990. Journal of the American College of Toxicology. 9(2): 165-83.

Scognamiglio J, Jones L, Letizia CS, and Api AM (2011). Fragrance material review on phenylethyl alcohol. Food Chem Toxicol. Oct 19. [Epub ahead of print].

Reproductive/ Developmental Toxicity

A study in which pregnant rats received 432mg/kg, 43mg/kg and 4.3mg/kg phenethyl alcohol (by gavage) on days 6-15 of gestation(with mild intoxication observed on administration of the highest dose) revealed that all pups from the highest group, 97 % of pups from the middle group and 55 % of pups from the lowest dose were either dead or malformed. The increase in malformations due to phenethyl alcohol was dose related (all pups from top dosage were malformed, 93% from the 43mg/kg group and 50% from the 4.3mg/kg group) [Brandt, 1990]. A similar study in which pregnant rats received oral doses of 508mg/kg phenethyl alcohol (in sunflower oil) on days 4 or 10-12 of pregnancy in contrast, did not reveal any developmental abnomalities [Brandt, 1990].

Exposure of pregnant female rats to concentrations of 1000, 3000 and 10 000 ppm phenethylalcohol in the diet was without effect on embryo-fetal loss, development or morphology [Brandt, 1990]. Incomplete ossification was however observed in animals given 10,000 ppm phenethyl alcohol.

A study in which 0.14, 0.43 and 1.4ml/kg phenethyl alcohol was applied to the skin of 35 pregnant rats (days 6-15 of pregnancy for 24 hr/day) and sacrificed at day 20 revealed maternal toxicity (3 mothers died after 6 days) and fetal abnormalities at 1.4ml/kg. Foetuses showing reduced ossification were greater in the 0.43ml/kg treated group than in the controls. Structural changes were also greater in 0.14 ml/kg treated group in comparison with the control group. A similar study in which the effect of dermal application of 0.07, 0.14, 0.28, 0.43 and 0.7ml/kg/day phenethyl alcohol to pregnant rats was observed revealed a no observed adverse effect level of 0.43ml/kg/day for cervical rib malformation. This value was used to estimate a safe use level for humans of 1% (in cosmetics) [Brandt, 1990].

Johnson et al., (1988) reported 2-phenethyl alcohol to have a adult/developmental ratio of 1.3 (Developmental Hazard Index) in the hydra assay which has been recognised as an assay thought to correctly identify substances that may be hazardous in utero. Ratios □ 3 usually undergo further mammalian testing [Johnson et al., 1988].

References - Reproductive/ Developmental Toxicity

Brandt (1990). Final report on the safety assessment of phenethyl alcohol, 1990. Journal of the American College of Toxicology. 9(2): 165-83.

Johnson et al., (1988). An analysis of the Hydra assay's applicability and reliability as a developmental toxicity pre-screen. Journal of the American College of Toxicology. 7:111.

Inhalation Toxicity

Human inhalation of phenethyl alcohol boiling vapour was reported to cause slight headache. However, 6 rats exposed to air saturated with phenethyl alcohol for 8h resulted in death [BIBRA, 1988]. It has also been reported that addition of 0.4 % phenethyl alcohol into a nasal spray did not induce any additional nasal irritation on repeated usage (study involved 16 volunteers) [BIBRA, 1988].

References - Inhalation Toxicity

BIBRA (1988). Phenylethyl alcohol. TNO BIBRA Toxicity profile.

Cardiac Toxicity

No data identified.

References - Cardiac Toxicity

No data identified.

Addictive Data

No data identified.

References - Addictive Data

No data identified.

Behavioral data

Umezu et al., (2002) reported on a study investigating alleged pharmacologically active constituents of rose oil, which contains 2-phenethyl alcohol, in mice. They concluded that 2-phenethyl alcohol produced ‘anti-conflict effects’ and that it an ‘anti-anxiety effect’ [Umezu et al., 2002].

Rose oil has traditionally been used to treat psychiatric disorders, but the scientific basis of this treatment remains poorly understood. The main odor component of rose oil is 2-phenylethanol (2-PE), but the neuropsychological effects of 2-PE have not been investigated in detail. Thus, they aimed to investigate the effects of 2-PE on mouse behavior. They first investigated whether 2-PE is attractive or repulsive to mice. After 2-PE inhalation, the mice underwent a series of behavioral experiments, such as the elevated plus maze, open field, Y-maze, tail-suspension, and Porsolt forced-swim tests. Mice did not have a strong interest in 2-PE but were not repelled by it nor were fearful. In the open field test, mice that had inhaled 2-PE spent less time in the center area, while in the tail suspension test, their immobility time decreased. There was no change in cognitive function, activity level, muscle strength, or aggression in these mice. Their results suggest that 2-PE elicits neuropsychological effects that alter the behavior of mice and may also elicit anti-depressive effects. Inhalation of rose oil containing 2-PE may be effective against depression and stress-related diseases [Ueno, et al., 2019].

References - Behavioral data

Umezu et al., (2002). Anticonflict effects of rose oil and identification of its active constituents. Life Sciences 72(1): 91-102.

Ueno, H., Shimada, A., Suemitsu, S., Murakami, S., Kitamura, N., Wani, K., ... & Ishihara, T. (2019). Anti-depressive-like effect of 2-phenylethanol inhalation in mice. Biomedicine & Pharmacotherapy, 111, 1499-1506.

In Vivo - Other Relevant Studies

The probable oral lethal dose of phenethyl alcohol is between 0.5-5g/kg or between one ounce and 1 pint for a 70kg human [Brandt, 1990].

Phenylethyl alcohol is reported as safe in cosmetic products in the present practices of use at concentrations up to 1% [Brandt, 1990].

The administration of doses greater than 0.3 g/kg [intraperitoneal] to mice is usually lethal however, the i.v injection of 1.83g phenethyl alcohol to a fox terrier dog [weighing 9 kg] was observed to initially produce depression and a lack of muscular coordination which then subsided as the dog became more excitable. Retching movements were initially observed which disappeared 2 hours after the initial injection. No effects were evident after a period of 12 hours [Brandt, 1990].

Phenethyl alcohol is metabolised in the rabbit to phenylacetic acid. In humans this is excreted in the urine as the conjugate phenacetylglutamine [Brandt, 1990; BIBRA, 1988]. Humans are reported to excrete 250-500 mg/day. This represents 25% of the total excretion of bound amino acids.

A study using radiolabelled phenylethyl alcohol revealed that the application of 0.14 and 1.4g/kg bw to rat skin for 24 h leads to the urinary excretion of 63 and 66% respectively, within a 24 hr period [BIBRA, 1988].

Allyl isothiocyanate (AIC) when used as a nasal trigeminal stimuli decreased the olfactory thresholds of 20 subjects (no further information provided) causing an increase in olfactory sensitivity to phenyl ethyl alcohol and butanol [Jacquot et al., 2004].

Figure 6: extract from Scognamiglio et al., (2012). Summary table of eye irritation studies:

Dose (%)	Vehicle	Reactions
100	N/A	Cornal opacities: mean ocular irritation score of 18.17 at 24hr
25	Ethanol	Cornal opacity, iris congestion,

moderate to severe conjunctival irritation
1 Not specified Minimal to moderate conjunctival irritation; transient iritial inflammation in 1/3 rabbits.

Figure 1: extract from Scognamiglio et al., (2012). Summary table of repeat dose studies:

Method	Dose	Species	Results
90 day repeated dose	0.25, 0.5, 1, and 2 g/kg/d topically applied	Rat	NOEL 0.5 g/kg/d
56-Week repeated dose	0.12% in drinking water	Rat	No significant differences from controls
4-Month repeated dose	50.8 mg/kg/d in sunflower oil	Rat	Increased serum cholinesterase and alanine aminotransferase; decreased serum protein.

References - In Vivo - Other Relevant Studies

Brandt (1990). Final report on the safety assessment of phenethyl alcohol, 1990. Journal of the American College of Toxicology. 9(2): 165-83.

BIBRA (1988). Phenylethyl alcohol. TNO BIBRA Toxicity profile.

Jacquot et al., (2004). Influence of nasal trigeminal stimuli on olfactory sensitivity. Critical Reviews of Biology. 327(4): 305-311.

Scognamiglio J, Jones L, Letizia CS, and Api AM (2011). Fragrance material review on phenylethyl alcohol. Food Chem Toxicol. Oct 19. [Epub ahead of print].

In Vitro Data

In Vitro Carcinogenicity/Mutagenicity

Assay Type	Species & Cell Line	Results
- Sister chromatid	Human lymphocyte	Negative [0.1-1.5mM] exchange[Highest conc. Was toxic to cultures, Brandt, 1990]
-AMES (+ /-Activation) mammalian microsome mutagenicity test	Salmonella typhimurium TA1535, TA1537, TA98 TA100	Negative, 3µmol/plate [Brandt, 1990]
- DNA-polymerase deficient assay [without activation]	Escherichia coli	Negative, no dose given, [Brandt, 1990]

Figure 7: extract from Scognamiglio et al., (2012). Summary table of bacterial studies.

Phenethyl alcohol at 0.25% inhibited the repair of radiation-induced single strand breaks in Escherichia coli

[Brandt, 1990].

References - In Vitro Carcinogenicity/Mutagenicity

Brandt (1990). Final report on the safety assessment of phenethyl alcohol, 1990. Journal of the American College of Toxicology. 9(2): 165-83.

In Vitro - Other Relevant Studies

Phenylethyl alcohol has also been shown to penetrate excised human abdominal skin at 0.65 mg/cm2/hr from an undiluted liquid and 0.260 mg/cm2/hr from a saturated aqueous solution however; this is reduced to 0.027 mg/cm2/hr from pure vapour and 0.021 mg/cm2/hr from a vaporized saturated aqueous solution [BIBRA, 1988].

References - In Vitro - Other Relevant Studies

BIBRA (1988). Phenylethyl alcohol. TNO BIBRA Toxicity profile.

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 phenethyl alcohol at levels up to 2 ppm, “did not increase the overall toxicity of cigarette smoke” [Carmines, 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 Phenethyl Alcohol at 26 ppm, 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.

A mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including phenethyl alcohol at 2 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].

When tested at 2 ppm in cigarettes, in a 13-week inhalation study, the presence of phenethyl alcohol “…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)].

A 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 phenethyl alcohol at 2 ppm, 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].

The addition of phenethyl alcohol at 47 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 phenethyl alcohol 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].

Roemer et al., (2002) reported on a study in which cigarettes containing various additives in three different combinations were produced. Smoke condensates prepared from these cigarettes were then tested in two different in vitro assays. The mutagenicity of the smoke condensate was assayed in the Salmonella plate incorporation [Ames] assay with tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of an S9 metabolic activation system. The cytotoxicity of the gas/vapour phase and the particulate phase was determined in the neutral red uptake assay with mouse embryo BALB/c 3T3 cells. The authors concluded that the in vitro mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients which included phenethyl alcohol at levels up to 2 ppm [a multiple of its typical use in a US cigarette] [Roemer et al., 2002].

Baker et al., [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of flavourings and casings, were added in different combinations to reference cigarettes. The addition of phenethyl alcohol at 47 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, in vitro micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker et al., 2004].

A total of 95 ingredients were tested individually through addition at different concentrations to the tobacco of experimental cigarettes. Mainstream cigarette smoke chemistry analysis, bacterial mutagenicity testing, and cytotoxicity testing were conducted. The authors concluded that these ingredients, which included phenethyl alcohol applied at levels up to 10,000 ppm on cigarettes produced minimal changes in the overall toxicity profile of mainstream cigarette smoke, and in some cases, the addition of high levels of an ingredient caused a small reduction in toxicity findings, probably due to displacement of burning tobacco [Gaworski et al., 2011].

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 phenethyl alcohol at levels up to 9 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

References - Emissions and Associated Toxicity Data

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

Carmines E. L. (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 1: Cigarette design, testing approach, and review of results. Food and 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.

Gaworski et al., (2011). An evaluation of the toxicity of 95 ingredients added individually to experimental cigarettes: approach and methods. Inhalation Toxicology: 1-12.

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

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.

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