Toxicological profile for

Ethyl oenanthate

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

Not applicable.

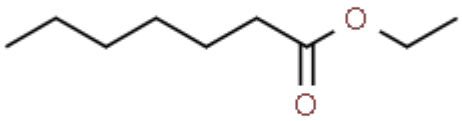
1.2. Synonyms

Ethyl heptanoate; N]; Aether Oenanthieus; Ethyl n-Heptoate; Ethyl oenanthate; Ethylheptanoat; Heptanoic acid, ethyl ester [ACD/Index Name]; Oil of Grapes; 4-02-00-00960 (Beilstein Handbook Reference) [Beilstein]; Aether oenanthicus; Cognac oil; Enanthic acid ethyl ester; Ethyl ester of heptanoic acid; Ethyl heptanoic acid; Ethyl heptoate; Ethyl heptoic acid; Ethyl heptylate; Ethyl n-heptanoate; Ethyl N-heptanoic acid; Ethyl oenanthylate; Ethylheptanoate; Grape oil; Heptanoic acid ethyl ester; Heptanoic acid-ethyl ester; Oleum vitis viniferae; Wine oil (ChemSpider)

1.3. Molecular formula

$C_9H_{18}O_2$ (ChemSpider)

1.4. Structural Formula



(ChemSpider)

1.5. Molecular weight (g/mol)

Not applicable.

1.6. CAS registration number

8016-21-5

1.7. Properties

1.7.1. Melting point

(°C): - 66 (ChemSpider)

1.7.2. Boiling point

(°C): 188-189 °C , 14 °C / 78 mmHg (77.7022 °C / 760 mmHg) (ChemSpider)

1.7.3. Solubility

No data available to us at this time.

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): No data available to us at this time.

1.7.6. Flammability limits (vol/vol%)

66 °C (ChemSpider)

1.7.7. (Auto)ignition temperature

(°C): No data available to us at this time.

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

No data available to us at this time.

1.7.10. Vapor pressure

No data available to us at this time.

1.7.11. log Kow

No data available to us at this time.

2. General information

2.1. Exposure

Cosmetics: Yes (Cosing)

Food: Yes (Burdock GA, 2010)

Environment: No evidence

Pharmaceuticals: No evidence

The estimated intakes from use as flavourings in the USA are 0.6214 and 0.7909 mg/kg bw/day for green cognac oil and white cognac oil, respectively.

Reported levels from use as a flavouring: (FEMA, 1994)

Green cognac oil	**White cognac oil**

Food category	Usual (ppm)	Max (ppm)	Food category	Usual (ppm)	Max (ppm)
Alcoholic beverages	215-40	240.50	Alcoholic beverages	4.29	12.32
Baked goods	39.25	55.65	Baked goods	20.27	37.31
Chewing gum	3.67	45.31	Chewing gum	22.01	637.70
Condiments, relishes	0.79	1.68	Fats, oils	0.75	1.15
Frozen dairy	34.49	47.26	Frozen dairy	5.93	15.91
Gelatins, puddings	25.71	42.06	Gelatins, puddings	5.93	24.35
Gravies	0.35	0.75	Gravies	-	-
Hard candies	6.73	8.41	Hard candies	1.04	1.65
Nonalcoholic beverages	6.04	38.85	Nonalcoholic beverages	3.55	8.11
Soft candy	33.17	46.16	Soft candy	6.21	17.46

As taken from Burdock, 2010.

Vitis vinifera leaf oil (CAS RNs 85594-37-2/84929-27-1/8016-21-5) is used as a fragrance ingredient in cosmetics in the EU. As taken from CosIng (undated).

Reported as used in fragrance compounds (IFRA; US EPA InertFinder Database.

Cognac oil green (no CAS RN given) is used as a flavour enhancer and grape seed oil (no CAS RN given) as a diluent, oleaginous vehicle and skin-conditioning agent in non-medicinal natural health products (Health Canada, 2021).

2.2. Combustion products

Pyrolysis and thermal degradation are assumed, no maximum exposure can be estimated for the ingredient.

This ingredient was investigated in a pyrolysis study. Results are given in Baker and Bishop (2005) J. Anal. Appl. Pyrolysis 74, pp. 145–170.

Ingredient Name & CAS Number	Max. cig. appln. level (ppm)	Purity of Sample (%)	Composition of pyrolysate (Compound, %)	Max. level in smoke (nü¡g)
Cognac oil, green 8016-21-5	10	na	Ethyl caproate (39.2) Ethyl Laurate (29.3) Ethyl palmitate (10.2) Ethyl myristate (6.0)	2 1 0.5 0.3

			Ethyl octanoate and/or ethyl acrylate (5.2)	0.3

2.3. Ingredient(s) from which it originates

Green cognac oil is formed during the fermentation of yeast and other sediments in wine lees or from other expressed residual cakes. White cognac oil is obtained by rectifying raw cognac oil (Burdock GA, 2010).

Vitis vinifera (grape) leaf oil is “derived from the leaves of the grape Vitis vinifera” (Fiume et al. 2014).

“Vitis vinifera leaf oil (CAS RNs 85594-37-2 / 84929-27-1 / 8016-21-5) is the essential oil derived from the leaves of the grape, Vitis vinifera L., Vitaceae.”

As taken from CosIng (undated).

Wine lees oil is produced from the particles of autolyzed yeast and grape skins, called wine lees, a by-product in the manufacture of cognac (eau-de-vie de vin). Traditionally, cognac, developed in the early seventeenth century, is obtained by double distillation of wine from the Cognac region of France (Lurton et al., 2012). Both green and white wine lees oils are obtained from steam distillation of wine lees, with the color dependent on the processing conditions.

Rosol, Thomas J et al. (2023) “FEMA GRAS assessment of natural flavor complexes: Lemongrass oil, chamomile oils, citronella oil and related flavoring ingredients.” Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association vol. 175 (2023): 113697. doi:10.1016/j.fct.2023.113697

3. Status in legislation and other official guidance

Use in food is approved in the EU and the US (182.50).

ADI: No ADI identified.

A website reports that the US Government has approved the use of cognac (white and green) oil as a tobacco additive, and that it occurs naturally in cognac brandy, and is used in alcoholic beverages, ice cream and baked goods (Anon).

Cognac, green, oil (CAS RN 8016-21-5) is included on the US FDA’s list of substances added to food (formerly EAFUS) as a flavouring agent or adjuvant and is generally recognized as safe (GRAS) under 21 CFR 182.50 (Certain other spices, seasonings, essential oils, oleoresins, and natural extracts) (FDA, 2024).

Codex Alim.: Not listed

C of E no.: 485

FEMA no.: 2331; 2332

TLV / OEL: Not listed

Cosmetics (UK): Not listed in Schedule 1

“Oils, cognac” (CAS RN 8016-21-5) are not registered under REACH (ECHA).

“Oils, cognac” (CAS RN 8016-21-5) are not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2025).

Cognac oil, green (CAS RN 8016-21-5) is listed in the US EPA InertFinder Database as approved for food, non-food and fragrance use pesticide products.

Oils, cognac (CAS RN 8016-21-5) are listed in the US EPA Toxic Substances Control Act (TSCA) inventory and also in the US EPA 2024 CDR list (Chemical Data Reporting Rule).

US EPA Substance Registry Services (SRS) Cognac, green, oil and cognac, white, oil (both CAS RN 8016-21-5; FEMA nos 2331 and 2332, respectively) have been designated as GRAS (generally recognized as safe) for use in food by FEMA (Hall RL and Oser BL, 1965).

Grape seed oil (no CAS RN given) is classified as a natural health product (NHP) under Schedule 1 item 2 (extract) of the Natural Health Products Regulations (Health Canada, 2021).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

No data available to us at this time.

4.2. Absorption, distribution and excretion

No data available to us at this time.

4.3. Interactions

”Carbon tetrachloride (CCl4) and ionizing radiation are well known environmental pollutants that generate free radicals and induce oxidative stress. The liver is the primary and major target organ responsible for the metabolism of drugs, toxic chemicals and affected by irradiation. This study investigated the effect of grape seed oil (GSO) on acute liver injury induced by carbon tetrachloride (CCl4) in γ-irradiated rats (7Gy). CCl4-intoxicated rats exhibited an elevation of ALT, AST activities, IL-6 and TNF-α level in the serum. Further, the levels of MDA, NO, NF-κB and the gene expression of CYP2E1, iNOS and Caspase-3 were increased, and SOD, CAT, GSH-Px, GST activities and GSH content were decreased. Furthermore, silent information regulator protein 1 (SIRT1) gene expression was markedly down-regulated. Additionally, alterations of the trace elements; copper, manganese, zinc and DNA fragmentation was observed in the hepatic tissues of the intoxicated group. These effects were augmented in CCl4-intoxicated-γ-irradiated rats. However, the administration of GSO ameliorated these parameters. GSO exhibit protective effects on CCl4 induced acute liver injury in γ-irradiated rats that could be attributed to its potent antioxidant, anti-inflammatory and anti-apoptotic activities. The induction of the antioxidant enzymes activities, down-regulation of the CYP2E1, iNOS, Caspase-3 and NF-κB expression, up-regulation of the trace elements concentration levels and activation of SIRT1 gene expression are responsible for the improvement of the antioxidant and anti-inflammatory status in the hepatic tissues and could be claimed to be the hepatoprotective mechanism of GSO.” As taken from Ismail AF et al. 2016. J. Photochem. Photobiol. B 160, 1-10. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27085796

“The present study was planned to investigate the effect of methomyl or imidacloprid on the brain of male rats. The effect grape seeds oil as an antioxidant was also evaluated. Animals were administered orally with 1/10 and 1/20 of LD50 methomyl and imidacloprid with 17 and 450 mg /kg bw for four and eight weeks. Grape seeds oil with 4 ml/kg b.wt. was used for protection from methomyl and imidacloprid toxicity. Brain cortex and hippocampus oxidative stress (glutathione S transferase GST, glutathione peroxidase GPX, superoxide dismutase SOD, malondialdhyde MDA and nitric oxide NO), Na+,K+, ATPase and acetyl-cholinesterase AChE were determined. The result showed that GST, GPX, MDA, and NO2 were increased significantly. But SOD, Na+K+ATPase and AChE were significantly reduced in comparison with the control. Grape seed oil induced a significant improvement for the pesticides brain toxicity but not to the level of control. The study suggested that the oil antioxidants not improve the brain toxicity induced by methomyl or

imidacloprid." As taken from Moeen D et al. 2018. J. Sci. Res. Sci. 35, 250-272. Available at https://jsrs.journals.ekb.eg/article_25535_48fc7b9825c461aa3f367c77cfa9b595.pdf

"The present study was conducted to assess the possible protective effects of grape seed oil on testis toxicity induced by Lead (Pb) in male rats. Four groups of rats were used in this experiment. Rats of the first group were served as control. The second group of rats was exposed to Pb (100 mg/kg) three times weekly. Rats of the third group were treated with grape seed oil (600mg/kg body weight/day) plus Pb. The fourth group was supplemented with grape seed oil at the same dose given to group three. After six weeks, the histopathological alterations were estimated. The testicular structure of rats exposed to Pb revealed some histological changes. The findings of this work indicated that grape seed oil slightly attenuated the histological alterations induced by Pb. Furthermore, the result of the present study suggests that the antioxidant properties of grape seed oil could be attributed to the protective effect against toxicity induced by Pb." As taken from Alawi NA et al. 2018. Advances in Biological Research 12 (1), 16-25. Available at https://bit.ly/2FtFOl2

5. Toxicity

5.1. Single dose toxicity

Species	**Route**	**Dose data**	**Source**
Mouse	Oral	LD_{50}: > 5000 mg/kg bw	Fd Cosmet. Toxicol. 13, 769, 1975
Guinea pig	Dermal	LD_{50}: > 5000 mg/kg bw	Fd Cosmet. Toxicol. 13, 769, 1975

As taken from RTECS, 1998.

5.2. Repeated dose toxicity

No data available to us at this time.

5.3. Reproduction toxicity

No data available to us at this time.

5.4. Mutagenicity

No data available to us at this time.

5.5. Cytotoxicity

"Physicochemical, bioactive, and antimicrobial properties of different cold press edible oil byproducts (almond (AOB), walnut (WOB), pomegranate (POB), and grape (GOB)) were investigated. ……. Almond and pomegranate byproduct extracts showed antibacterial activity depending on their concentration, whereas those of walnut and grape byproducts showed no antibacterial activity against any pathogenic bacteria tested. According to the results of the present study, walnut, almond, pomegranate, and grape seed oil byproducts possess valuable properties that can be taken into consideration for improvement of nutritional and functional properties of many food products." As taken from Karaman S et al. 2015. J. Agric. Food Chem. 63(8), 2305-13. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25647068

5.6. Carcinogenicity

No data available to us at this time.

5.7. Irritation/immunotoxicity

The neat material was not irritating to mouse skin (Urbach and Forbes, 1974) but, after 24-hour covered contact, was slightly irritating to rabbit and guinea pig skin (Moreno, 1974).

Not irritating or sensitizing to human skin after 48-hour covered contact at 4% (Kligman, 1974).

“Tocotrienols are unsaturated forms of vitamin E previously shown to reduce adipogenesis and adipose inflammation. In this study, muscadine grape seed oil (MGSO) was identified as a novel source of tocotrienols containing significant amounts of α- and γ-tocotrienol (T3) with minor seasonal changes. The aim of this study was to assess the anti-adipogenic and anti-inflammatory potential of MGSO by using primary human adipose-derived stem cells (hASCs). Differentiating hASCs were treated with MGSO and compared with rice bran and olive oil. Accumulation of triglyceride was significantly lower in MGSO-treated hASCs than rice bran and olive oils. A tocotrienol rich fraction (TRF) from MGSO was prepared by solid phase extraction and eluted with 15% 1,4-dioxane in hexane. The MGSO-derived TRF treatment significantly reduced mRNA and protein expression that are crucial to adipogenesis (e.g., PPARγ and aP2) in hASCs. Furthermore, TRF from MGSO markedly reduced LPS-induced proinflammatory gene expression in human adipocytes and cytokine secretion to the medium (IL-6 and IL-8). Collectively, our work suggests that MGSO is a stable and reliable natural source of T3 and MGSO may constitute a new dietary strategy to attenuate obesity and its associated adipose inflammation.” As taken from Zhao L et al. 2015. Food Funct. 6(7), 2293-302. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26073057

5.8. All other relevant types of toxicity

No phototoxic effects were reported (Urbach and Forbes, 1974).

Total particulate matter (TPM) from heated (tobacco or nicotine) product(s) containing Cognac Oil was tested in a battery of in vitro and/or in vivo test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the TPM was not increased by the addition of Cognac Oil when compared to TPM from 3R4F cigarettes. The table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
In vitro genotoxicity	305	JTI KB Study Report(s)
In vitro cytotoxicity	305	JTI KB Study Report(s)

“Tocotrienols are unsaturated forms of vitamin E previously shown to reduce adipogenesis and adipose inflammation. In this study, muscadine grape seed oil (MGSO) was identified as a novel source of tocotrienols containing significant amounts of α- and γ-tocotrienol (T3) with minor seasonal changes. The aim of this study was to assess the anti-adipogenic and anti-inflammatory potential of MGSO by using primary human adipose-derived stem cells (hASCs). Differentiating hASCs were treated with MGSO and compared with rice bran and olive oil. Accumulation of

triglyceride was significantly lower in MGSO-treated hASCs than rice bran and olive oils. A tocotrienol rich fraction (TRF) from MGSO was prepared by solid phase extraction and eluted with 15% 1,4-dioxane in hexane. The MGSO-derived TRF treatment significantly reduced mRNA and protein expression that are crucial to adipogenesis (e.g., PPARγ and aP2) in hASCs. Furthermore, TRF from MGSO markedly reduced LPS-induced proinflammatory gene expression in human adipocytes and cytokine secretion to the medium (IL-6 and IL-8). Collectively, our work suggests that MGSO is a stable and reliable natural source of T3 and MGSO may constitute a new dietary strategy to attenuate obesity and its associated adipose inflammation." As taken from Zhao L et al. 2015. Food Funct. 6(7), 2293-302. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26073057

"Physicochemical, bioactive, and antimicrobial properties of different cold press edible oil byproducts (almond (AOB), walnut (WOB), pomegranate (POB), and grape (GOB)) were investigated. ……. Almond and pomegranate byproduct extracts showed antibacterial activity depending on their concentration, whereas those of walnut and grape byproducts showed no antibacterial activity against any pathogenic bacteria tested. According to the results of the present study, walnut, almond, pomegranate, and grape seed oil byproducts possess valuable properties that can be taken into consideration for improvement of nutritional and functional properties of many food products." As taken from Karaman S et al. 2015. J. Agric. Food Chem. 63(8), 2305-13. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25647068

OBJECTIVE : Acarbose and trans-chalcone are glucosidase inhibitors whose beneficial effects have been demonstrated in diabetes. The present study aimed at investigating their potential effects in obesity. MATERIALS AND METHODS: NMRI male mice (n = 48) were subjected to a high fat diet for four weeks, which induced an initial state of obesity. One control group was given normal rodent diet. Obese animals were then switched to normal rodent diet, and divided to four groups (n = 12 in each): untreated, sham (receiving grape seed oil), and experimental groups receiving acarbose and trans-chalcone (12 mg/kg) during eight weeks. Body weight, blood glucose and other biochemical parameters including triglycerides (TG), cholesterol, HDL, AST, and ALT were measured, as well as leptin, adiponectin, TNF-α, and total antioxidant capacity (TAC). Histological studies were performed on adipose cells and liver tissue samples. RESULTS: ……. Grape seed oil, used as a solvent for trans-chalcone was found to possess significant effect on TG and TAC, and had beneficial effects on other factors including liver enzymes and cholesterol. ….. All compounds seemed to be able to affect fat deposition in liver tissue, and decrease the size of adipose tissue cells to some extent. CONCLUSION: In conclusion, the tested compounds were able to affect lipid accumulation in tissues and influence adipokines, which may result in an enhanced state with regard to inflammation and oxidative stress." As taken from Jalalvand F et al. 2015. Arch. Endocrinol. Metab. 59(3), 202-9. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26154086

6. Functional effects on

6.1. Broncho/pulmonary system

No data available to us at this time.

6.2. Cardiovascular system

"The purpose of this study was to evaluate the effect of the consumption of seed oils from Vitis vinifera and Arachis hypogaea in platelet aggregation. The initial hypothesis suggested that subjects who have consumed these seed oils undergo modified platelet aggregation. This study was performed using a pre-post test design, with a control group, and double blind. The effects of the consumption of grape seed and peanut oils were measured for platelet aggregation in clinical and laboratory tests in 30 healthy subjects. In addition to this group, a control group of 4 health

subjects received no treatment with oils, just 500 mg oral administration acetylsalicylic acid for 7 days. Platelet aggregation was assessed by the Born turbidimetric method, using 3 different concentrations of adenosine diphosphate as agonists (2, 54; 1, 17; and 0, 58 μM). The study subjects had very similar results; both oils were shown to have a significant reduction in platelet aggregation. Grape seed oil showed a decrease of 8.4 ± 1% in aggregation, compared with peanut oil, which decreased aggregation by 10.4 ± 1%. The control group, taking 500 mg OD aspirin for 7 days, showed a significant decrease in platelet aggregation, similar to that of oil ingestion. Each of the oils was analyzed for fatty acids, to determine which particular acids were presents in greater levels, which could explain the reduction in platelet aggregation. The oil found to be most abundant in grape seeds was linoleic acid (omega-6), and in peanuts, it was oleic acid (omega-9). However, in fact, both acids reduced platelet aggregation. Consumption of plant oils from grape seeds and peanuts had a lowering effect on platelet aggregation, in addition to containing a high content of unsaturated fatty acids. However, omega-3, omega-6, and omega-9 fatty acids were not specifically responsible for the reductions mentioned above." As taken from Bazán-Salinas IL et al. 2016. Am. J. Ther. 23(6), e1315-e1319. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/25741817

"Consumptions of fruit seed oils and meals could potentially improve cardiovascular health by reducing plasma total cholesterol and low-density lipoprotein (LDL). The study objective was to compare the effectiveness of expeller-pressed and solvent-extracted grape, tomato, pomegranate seed oils, and defatted pomegranate meals in lowering plasma and hepatic cholesterol using hamster models. Hamsters were fed with fruit seed oils (FSO), defatted pomegranate seed meals (PDM), or control diets. After a 3-week feeding period, plasma total triglycerides of treatment diets were significantly lower. FSO also reduced total, very-low-density lipoprotein- (VLDL), and LDL-cholesterols, while PDM only lowered VLDL-cholesterols. Decreases in low-density and high-density lipoproteins (LDL/HDL) ratios were also observed in most treatments. In liver, triglycerides, total, and free cholesterol levels did not vary between control and treatments. There were no significant differences in lipid modulating properties between solvent-extracted and expeller-pressed oils. In conclusion, partial replacements of saturated fat in high-fat diets with tomato, pomegranate, and grape seed oils could effectively reduce plasma triglyceride levels and improve HDL/LDL ratios." As taken from Teh HE et al. 2019. J. Agric. Food Chem. 67(22), 6150-6159. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31117552/c

6.3. Nervous system

"This study investigated the possible beneficial effects of grape seed oil (GSO) on carbon tetrachloride (CCl4)-induced acute neurotoxicity in γ-irradiated rats. A statistical significant decrease in superoxide-dismutase (SOD), catalase (CAT), and glutathione-peroxidase (GPx) activities and reduced glutathione (GSH) content were exhibited. Further, a significant elevation in malondialdehyde (MDA), nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and transforming growth factor-beta-1 (TGF-β1) levels was observed. Furthermore, xanthine oxidase (XO) and inducible nitric oxide synthase (iNOS) gene expression were elevated in the γ-irradiated animals treated with an acute dose of CCl4. The pretreatment of GSO exerts significant amelioration of the studied parameters. In conclusion, this study demonstrated that GSO has a neuroprotective effect against CCl4-induced brain injury in γ-irradiated rats, which is likely attributed to its ability to scavenge the free radicals, suppress the inflammatory responses, improve the activity of the antioxidant enzymes and inhibit the XO and iNOS gene expression levels." As taken from Ismail AF et al. 2015. J. Photochem. Photobiol. B 153, 317-23. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26513383

6.4. Other organ systems, dependent on the properties of the substance

"Carbon tetrachloride (CCl4) and ionizing radiation are well known environmental pollutants that generate free radicals and induce oxidative stress. The liver is the primary and major target organ

responsible for the metabolism of drugs, toxic chemicals and affected by irradiation. This study investigated the effect of grape seed oil (GSO) on acute liver injury induced by carbon tetrachloride (CCl4) in γ-irradiated rats (7Gy). CCl4-intoxicated rats exhibited an elevation of ALT, AST activities, IL-6 and TNF-α level in the serum. Further, the levels of MDA, NO, NF-κB and the gene expression of CYP2E1, iNOS and Caspase-3 were increased, and SOD, CAT, GSH-Px, GST activities and GSH content were decreased. Furthermore, silent information regulator protein 1 (SIRT1) gene expression was markedly down-regulated. Additionally, alterations of the trace elements; copper, manganese, zinc and DNA fragmentation was observed in the hepatic tissues of the intoxicated group. These effects were augmented in CCl4-intoxicated-γ-irradiated rats. However, the administration of GSO ameliorated these parameters. GSO exhibit protective effects on CCl4 induced acute liver injury in γ-irradiated rats that could be attributed to its potent antioxidant, anti-inflammatory and anti-apoptotic activities. The induction of the antioxidant enzymes activities, down-regulation of the CYP2E1, iNOS, Caspase-3 and NF-κB expression, up-regulation of the trace elements concentration levels and activation of SIRT1 gene expression are responsible for the improvement of the antioxidant and anti-inflammatory status in the hepatic tissues and could be claimed to be the hepatoprotective mechanism of GSO." As taken from Ismail AF et al. 2016. J. Photochem. Photobiol. B 160, 1-10. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27085796

"BACKGROUND: Inflammatory bowel diseases contain two digestive system diseases, ulcerative colitis (UC) and Crohn's disease with unclear causes. The aim of present study was to investigate the therapeutic effects of administration of the Sesame oil (SO) and grape seed oil (GSO) as enema route in rats suffering from experimental acetic acid induced UC. METHODS: Eighty male rats were randomly allocated into 8 equal groups as health control (HC_1) without any disease treated with 1 ml of normal saline as enema; HC_2 received SO; HC_3 received GSO; negative control (NC) with induced UC receiving 1 ml of normal saline as enema; and positive control (PC) with induced UC treated by asacol. All treatments were performed identically with 4 mg/kg of medication except for asacol that was 100 mg/kg for 7 days. The weight changes was recorded after seven days. The serum levels of malondialdehyde (MDA), total antioxidant capacity (TAC), interleukin-6, and c-reactive protein (CRP) were measured. Colon macroscopic and microscopic histological changes were also measured at the end of 7^{th} day. RESULTS: No significant changes were detected in weight in neither groups on day 0 nor at the end of study. No beneficial effects were seen for all treatments regarding healing process and the decrease in inflammation. Between treatment groups, the lowest MDA (7.40±0.98 U/ml), CRP (83.20±10.01 mg/l) and IL-6 levels (130.86±10.70 mU/ml) and highest TAC (1.91±0.43 mmol/l) belonged to GSO group. CONCLUSION: GSO enema alone can be considered as a treatment of choice for UC due to its antioxidant properties". As taken from Hosseinzadeh F et al. 2017. World J. Plast. Surg. 6(2), 176-182. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/28713708

"This study aims to investigate the potential of virgin grape seed oil (VGSO) to improve insulin resistance and energy metabolism disorder in mice fed a high-fat diet. The results show that respiratory exchange rate and energy consumption in mice can be increased by the administration of VGSO. Insulin resistance is significantly alleviated by VGSO, which can be attributed to its protective effect on hexokinase and α-glucosidase activities and improvement in leptin resistance. The effect of refined grape seed oil (RGSO), RGSO reinforced with polyphenol, RGSO reinforced with unsaponifiables, and RGSO reinforced with polyphenol and unsaponifiables on oral glucose tolerance, homeostasis model assessment of insulin resistance and quantitative insulin sensitivity check index are determined and compared. The results suggest that polyphenol may be the most critical factor for regulating insulin resistance. Specific linear and polynomial equations are provided to explain the correlation between insulin resistance, energy metabolism, and hyperlipidemia. Practical Applications: The effects of virgin grape seed oil (VGSO) on insulin resistance and energy metabolism disorder in mice fed a high-fat diet were investigated. In addition, the key component in VGSO for regulating insulin resistance was preliminarily investigated. Furthermore, the correlations among fasting blood glucose, triglyceride/cholesterol concentration, and respiratory exchange

rate/energy consumption/activity level were investigated. This research will provide a theoretical basis for the development of functional edible oil for high blood lipid, cholesterol, and diabetes patients." As taken from Li X et al. 2020. European Journal of Lipid Science and Technology 122(4), 1900158. Available at https://onlinelibrary.wiley.com/doi/abs/10.1002/ejlt.201900158

"Background: The process of wound healing in the socket include the healing of wounds in soft tissues, and healing of the bone. The herbal medicament widely used in the healing of different wounds. The benefit of Grape seed oil due to their anti-oxidant and anti-inflammatory effect. Objective: Histological evaluation the effects of local application of grape seeds oil in the healing process of dental socket after tooth extraction and compared the result with normal healing process. Patients and Methods: Thirty six New Zeland male rabbits were used in this study, the upper right central incisor was extracted for each rabbit, then the rabbits were divided into 3 main groups; Control group: 12 rabbits, the socket heal spontaneously, sponge group: 12 rabbits, the socket treated with absorbable hemostatic sponge and grape seed oil group: 12 rabbits, the socket treated with local application of 0.5 ml/Kg of B.W. grape seeds oil fixed by absorbable hemostatic sponge. Then each group were divided into two sub group according to the healing intervals 2 and 4 week (6 rabbits from each group). Histological evaluation performed by section stained with hematoxylin and eosin (H&E), and histomorphometric analysis for assessment of osteoclasts, osteoblasts, osteocytes, trabecular no, trabecular area and marrow space area by Image J. software. Results: The histological and histomorphometric results of present study showed enhancement of healing process in grape seeds oil and sponge group after tooth extraction by activation of large number of osteoblasts, osteocytes and osteoclasts that started from apical part, then middle part finally in coronal part of the socket. Conclusion: Grape seed oil accelerate the healing process after locally treated tooth socket and assessed in new bone formation." As taken from Hassan MAA and Al-Ghaban N. 2019. Diyala Journal of Medicine 17(2), 70-84. Available at http://www.djm.uodiyala.edu.iq/index.php/djm/article/view/498

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al. 1994 & 1998).

Tobacco smoke condensates from cigarettes containing ethyl oenanthate and an additive free, reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of ethyl oenanthate. Table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
Smoke chemistry	2 (green, oil)	Carmines, 2002 & Rustemeier et al. 2002
	88	Baker et al. 2004a
	19.5 52 260	JTI KB Study Report(s)
	4,670	Gaworski et al. 2011 & Coggins et al. 2011b
	36	Roemer et al., 2014

In vitro genotoxicity	2 (green, oil)	Carmines, 2002 & Roemer et al. 2002
	88 (green)	Baker et al. 2004c
	19.5 80 (white oil) 260	JTI KB Study Report(s)
	60.7	fGLH Study Report (2010)
	4,670	Gaworski et al. 2011 & Coggins et al. 2011b
	36	Roemer et al., 2014
In vitro cytotoxicity	2 (green, oil)	Carmines, 2002 & Roemer et al. 2002
	88 (green)	Baker et al. 2004c
	19.5 80 (white oil) 260	JTI KB Study Report(s)
	60.7	fGLH Study Report (2010)
	4,670	Gaworski et al. 2011 & Coggins et al. 2011b
	36	Roemer et al., 2014
Inhalation study	<0.1	Gaworski et al. 1998
	2 (green, oil)	Carmines, 2002 & Vanscheeuwijck et al. 2002
	88 (green)	Baker et al. 2004c
	19.5 80 (white oil)	JTI KB Study Report(s)
	36	Schramke et al., 2014
Skin painting	<0.1 (white)	Gaworski et al. 1999
	19.5	JTI KB Study Report(s)
In vivo genotoxicity	36	Schramke et al., 2014

9. Heated/vapor emissions toxicity

Total particulate matter (TPM) from heated (tobacco or nicotine) product(s) containing Cognac Oil was tested in a battery of in vitro and/or in vivo test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the TPM was not increased by the addition of Cognac Oil when compared to TPM from 3R4F cigarettes. The table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
In vitro genotoxicity	305	JTI KB Study Report(s)
In vitro cytotoxicity	305	JTI KB Study Report(s)

10. Ecotoxicity

10.1. Environmental fate

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cognac oils are of uncertain persistence in the environment.

Data accessed May 2017 on the OECD website.

10.2. Aquatic toxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that oils, cognac are not inherently toxic to aquatic organisms and are of low ecotoxicological concern.

Data accessed May 2017 on the OECD website.

10.3. Sediment toxicity

No data available to us at this time

10.4. Terrestrial toxicity

No data available to us at this time.

10.5. All other relevant types of ecotoxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that cognac oils are of uncertain bioaccumulative potential in the environment.

Data accessed May 2017 on the OECD website.

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12. Other information

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Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 37, 1996.

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications, Addendum 4. FAO Food and Nutrition Paper, No. 52, Add. 4, 1996.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme on Chemical Safety (IPCS).

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 6 to 15 February 1996. The meeting was opened by Dr J.L. Herrman, Scientist, International Programme on Chemical Safety, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Herrman noted that governments and the Codex Alimentarius Commission were increasingly relying on recommendations of the Committee relating to the safety of food additives and contaminants. Several substances on the agenda of the present meeting involved difficult issues of a general nature and would require new approaches if useful advice was to be provided.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been forty-five previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendations made at the forty-fourth meeting (Annex 1, reference *116*).

The tasks before the Committee were:

(a) to elaborate further principles for evaluating the safety of food additives and contaminants (section 2);
(b) to undertake toxicological evaluations of certain food additives and contaminants (section 3 and Annex 2);
(c) to review and prepare specifications for selected food additives (sections 3 and 4 and Annex 2); and
(d) to assess dietary intake of aflatoxins and estimate the potential risks for different human populations (section 4).

2.1 Modification of the agenda

Salatrim, a fat substitute, was removed from the agenda at the request of the manufacturer.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants*

in food (Annex 1, reference *76*), as well as principles elaborated subsequently at meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94*, *101*, *107* and *116*), including the present one. Environmental Health Criteria, No. 70 (Annex 1, reference *76*) embraces the major observations, comments and recommendations on the safety assessment of food additives and contaminants contained, up to the time of its publication, in the reports of the Committee and other associated bodies. The Committee noted that the document reaffirms the validity of recommendations that are still appropriate, and points out the problems associated with those that are no longer valid in the light of modern technical advances.

2.2.1 *Procedure for the safety evaluation of flavouring agents*

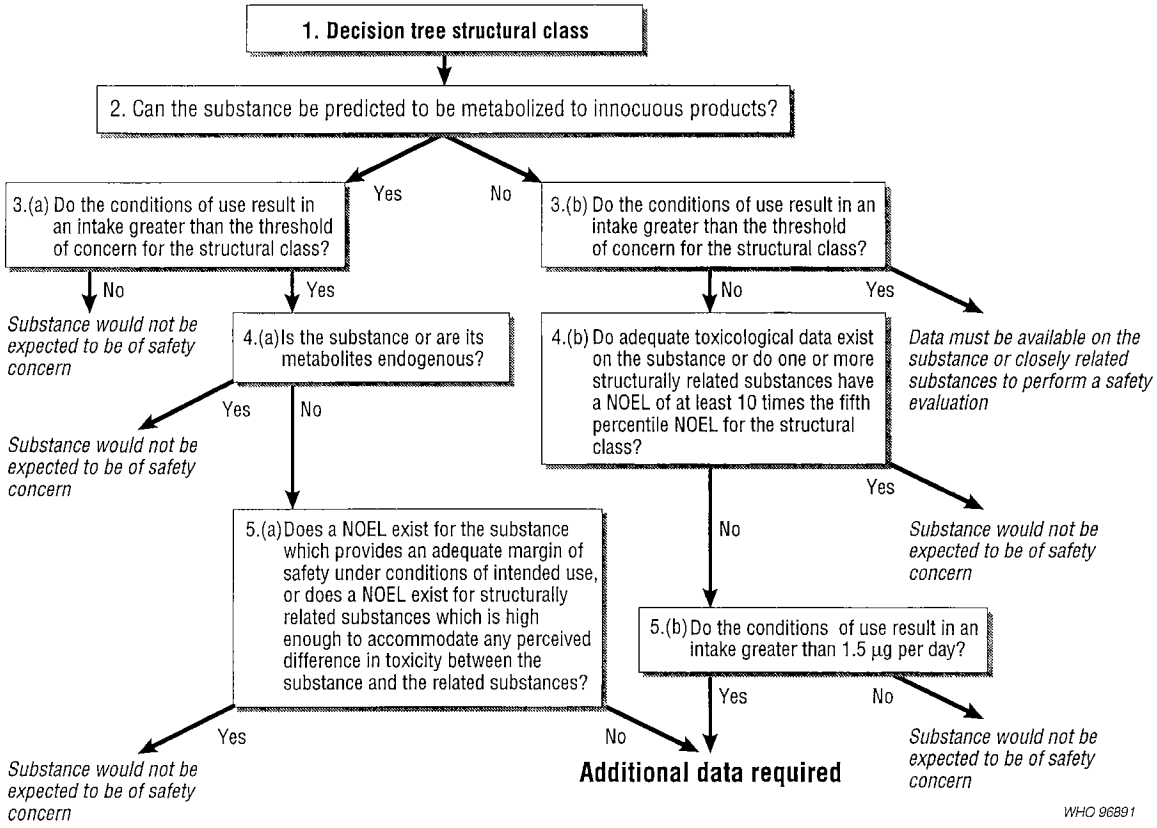
The Committee evaluated three groups of flavouring agents. It used a procedure based on that reviewed at the forty-fourth meeting of the Committee (Fig. 1; Annex 1, reference *116*, section 2.2.1). The approach incorporates a series of criteria designed to provide a means of evaluating such agents in a consistent and timely manner. The criteria, which were drawn up in the light of the principles for the safety evaluation of flavouring substances (Annex 1, reference *76*), take account of available information on intake from current uses, structure–activity relationships, and metabolism and toxicity data. They incorporate procedures outlined in the report of the thirty-third meeting of the Committee (Annex 1, reference *83*), which include a method for dividing flavouring substances up into three structural classes based on structural characteristics and metabolism. The use of these criteria provides a means of ranking flavouring substances in terms of concern over potential inherent toxicity and provides guidance on the nature and extent of the data required to perform a safety evaluation.

The criteria take advantage of the fact that some flavouring agents occur as normal constituents of mammalian tissues or are metabolized to form such constituents, and are then completely metabolized to innocuous end-products such as carbon dioxide and water. Flavouring agents with these characteristics are considered to be safe for consumption if human intake is low, but are evaluated on the basis of toxicity data if human intake is high. The safety evaluation may involve the use of toxicity data on the individual substance concerned or may rely, at least in part, on toxicity data on substances of closely related structure.

For flavouring agents that are not known to be metabolized to innocuous end-products, the safety evaluation must be based on toxicity data, even if intake is low. In such cases, there must be an adequate

Figure 1

Safety evaluation procedure reviewed at the forty-fourth meeting of the Committee[a]



[a] Reproduced, with minor editorial changes and modification of the numbering, from Annex 1, reference *117*.

margin of safety between human intake of the flavouring agent and the no-observed-effect level (NOEL) for the substance or the NOEL for a substance of closely related structure on which the safety evaluation relies.

For those flavouring agents currently in use for which no toxicity or metabolic data exist, but where intake is extremely low, it might be possible to specify a threshold below which intake is considered safe (human intake threshold).

The procedure described above involves the integration of data on intake, in relation to the human intake threshold, with information on structure–activity relationships, metabolism and toxicity. The data on intake used in the procedure at the present meeting were derived from figures for the total annual production of flavouring agents used in food in Europe and the USA. Estimates of intake were based on the assumption that only 60% of the total amount used is reported and that the total amount used is consumed by only 10% of the population. The Committee noted that the evaluations performed using the procedure were based on the intake estimates available at the meeting and that changes in intake might warrant re-evaluation of a flavouring agent. The Committee recommended that information on intake should be periodically updated to ensure the validity of safety evaluations.

The Committee noted that the procedure is intended for application to flavouring agents used in food and not to other uses of these agents. It also noted that many flavouring agents are members of structurally related groups and that, in conformity with past practice, consideration should be given to evaluating the safety of such groups as a whole.

The Committee noted that the safety evaluation procedure is not intended to be applied to flavouring agents with existing unresolved problems of toxicity. As with any scheme, its application calls for judgement, and it should not replace expert opinion; the Committee therefore reserved the right to use alternative approaches when data on specific flavouring agents warranted such action.

It was noted that a key element of the procedure involves determining whether a flavouring agent and the products of its metabolism are innocuous and/or endogenous substances. The Committee considered that these terms require definition. It recommended that "innocuous metabolic products" should be defined as products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent, while "endogenous substances" are

intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included. The estimated intake of a flavouring agent that is, or is metabolized to, an endogenous substance should be judged not to give rise to perturbations outside the physiological range.

The Committee noted that Acceptable Daily Intakes (ADIs) had previously been established for some flavouring agents or groups of flavouring agents, and recommended that these should be retained, since the information on which they are based is relevant to an evaluation of their safety and, in addition, they may have food additive uses other than as flavouring agents.

Application of the procedure

In applying the procedure to the groups of esters considered during the meeting, the Committee noted that consideration should be given to both the parent compound and its metabolic products, and that these should be evaluated separately when necessary.

The Committee used the procedure to evaluate three groups of esters, namely ethyl esters, isoamyl esters and allyl esters. First, the substance is assigned to a structural class according to the decision tree of Cramer et al. (*2*; see Figure 1).

The structural classes are as follows:

- Class I. Substances that have simple chemical structures and efficient modes of metabolism which would suggest a low order of oral toxicity.
- Class II. Substances that have structural features that are less innocuous than those of substances in class I, but are not suggestive of toxicity. Substances in this class may contain reactive functional groups.
- Class III. Substances that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity.

The approach then differs, depending on whether the flavouring agent is predicted to be metabolized to innocuous products (step 2). For flavouring agents with high intakes (step 3(a)) that are metabolized to innocuous but not endogenous products (step 4(a)), the procedure requires a NOEL for the substance or a structurally related substance which provides an adequate margin of safety in relation to the estimated intake (step 5(a)). In contrast, for flavouring agents not predicted to be metabolized to innocuous products (step 2) and with

low intakes (step 3(b)), the procedure requires adequate toxicological data on the substance or on a structurally related substance (step 4(b)). The Committee concluded that the procedure should be modified (see Fig. 2), so that step 4(b) in Fig. 1 would read "Does a NOEL exist for the substance which provides an adequate margin of safety under conditions of intended use [(*3*) (Annex 1, reference *76*)], or does a NOEL exist for structurally related substances which is high enough to accommodate any perceived difference in toxicity between the substance and the related substances?" The Committee did not fully discuss the application of step 5(b) of the original procedure ("Do the conditions of use result in an intake greater than 1.5 μg per day?") to flavouring agents, and it was not considered at the present meeting.

The Committee found that the procedure provided a sound basis for evaluating the safety of the three groups of flavouring agents considered during the meeting and recommended that it should be used at future meetings to evaluate other groups of flavouring agents.

2.2.2 *Survival of rats in long-term studies*

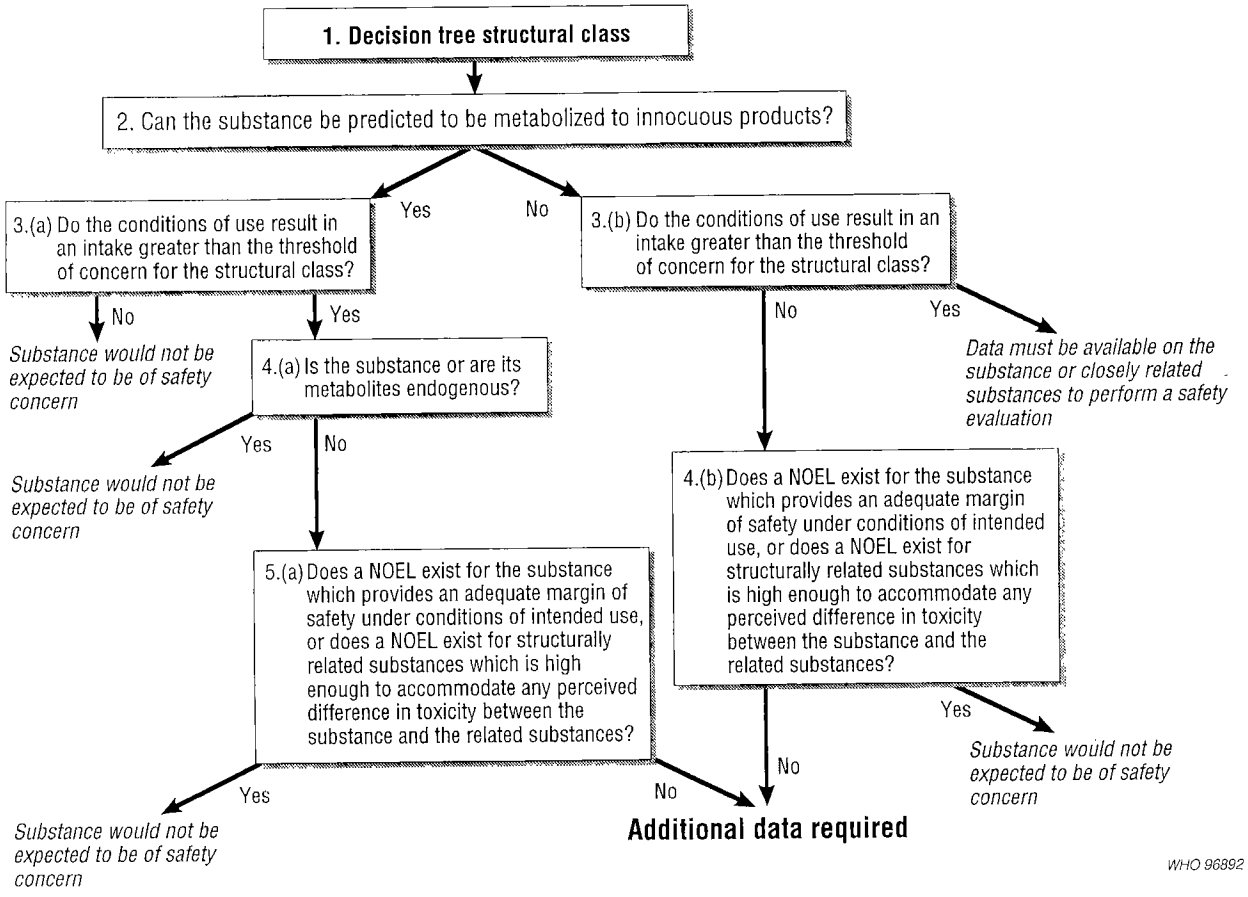
The Committee discussed the general issue of survival in contemporary long-term studies in experimental animals in response to the problems encountered in assessing the adequacy of the data on alitame (section 3.4). It recognized that increasingly poor survival rates have been seen in rats in long-term studies over the past 5–10 years. Furthermore, the background incidence of some tumours has increased, and this has been related to an increase in the body weight of commonly used strains of rats, possibly due to selective breeding. These factors have tended to complicate and in some cases confound the interpretation of long-term studies, particularly in relation to carcinogenesis. They indicate that the traditional carcinogenesis protocol is becoming increasingly difficult to carry out, and that caution should be exercised in using data on historical controls. The Committee considered that these factors should be taken into account in interpreting the results of contemporary studies, but do not necessarily negate the value of such studies. Studies that do not satisfy arbitrarily imposed criteria for survival and/or duration may still provide useful data for assessing the carcinogenic potential of a substance.

2.2.3 *Deadlines for submission of data*

It has been customary for the Secretariat to specify a deadline for the submission of data in announcing forthcoming meetings of the Committee. In recent years, such deadlines have increasingly been ignored, making it difficult to produce adequately reviewed

Figure 2

Safety evaluation procedure, as modified by the Committee at the present meeting



monographs in time for the meeting. The Committee therefore agreed that data submitted after the specified deadline would normally be considered at a later meeting.

The Committee again emphasized that requests for the modification of specifications must be supported by data. It will make changes only if it considers that adequate justification has been provided.

2.2.4 *Toxicological significance of proliferative lesions of the adrenal medulla in rats fed polyols and other poorly digestible carbohydrates*

Polyols (sugar alcohols) are used mainly as bulk sweetening agents and particularly as replacements for sugar. They include the monosaccharide-derived polyols mannitol, sorbitol and xylitol, and the disaccharide-derived forms maltitol, isomalt and lactitol, as well as polyol mixtures such as maltitol syrup and sorbitol syrup, which contain hydrogenated polysaccharides.

The polyols have appeared on the agenda at many meetings of the Committee, starting with the seventh meeting in 1963, when sorbitol was reviewed, and most recently at the forty-first meeting in 1993 (Annex 1, references *7*, *11*, *13*, *32*, *47*, *56*, *59*, *62*, *70*, *73*, *83* and *107*).

At its twenty-sixth meeting (Annex 1, reference *59*), the Committee concluded that the adrenal medullary hyperplasia seen in rats fed 20% sorbitol in the diet was the physiological consequence of the gross dietary and metabolic imbalances produced by the high levels of this substance in ageing rats, and recommended that the influence of carbohydrate intake on mineral metabolism be taken into account in assessing the possible toxicological significance of this effect.

At its twenty-seventh meeting (Annex 1, reference *62*), the Committee noted that the background incidence of these adrenal lesions in different strains of rat varied from 0% to 80%. It concluded that the high incidence of these lesions, their species-specificity, and their great variation within rat strains made it difficult to extrapolate the significance of the findings to humans in the absence of further information. At its forty-first meeting (Annex 1, reference *107*), the Committee recommended that the information database on adrenal medullary hyperplasia and phaeochromocytomas associated with polyols and other poorly absorbed carbohydrates be reviewed and that the mechanisms of appearance of these lesions and their toxicological significance be assessed at a future meeting.

At its present meeting, the Committee examined previously reviewed studies and those cited in a recent comprehensive review of all the relevant data (*4*).

Mutagenicity and genotoxicity studies. Mutagenicity and genotoxicity studies both *in vitro* and *in vivo* provided no evidence that any of the polyols has a mutagenic or genotoxic potential (Annex 1, references *72* and *74*).

Long-term studies in animals. Long-term studies in different strains of rats demonstrated that adrenal medullary hyperplasia and neoplasia develop in response to long-term administration of diets containing high levels of polyols (over 5% of the diet). In contrast, such lesions were not observed after long-term feeding of polyols to mice or dogs. The effect on the adrenal medulla of the rat thus appeared to be species-specific. The finding was not unique to polyols; lactose, another poorly digested carbohydrate, also produced such adrenal lesions in rats, but not in mice.

The effects of individual polyols and lactose in long-term studies in rats are summarized in Table 1.

Studies in humans. A number of studies have been conducted on the safety, cariogenicity, caloric value and metabolism of polyols in humans. The consumption of these polyols by human volunteers in controlled studies and by the public at large has not been associated with any significant adverse effects other than laxation at high doses. These studies show that even relatively high doses of polyols (of the order of 100 g per day), consumed for up to 5.3 years, have no effect on parameters that suggest adverse effects on energy metabolism, liver function or mineral homeostasis. For example, in two clinical studies designed to assess the overall safety of xylitol, in which male

Table 1
Main effects of polyols and lactose in long-term studies in rats

Substance	Effect[a]				
	Adrenal medullary hyperplasia or neoplasia	Caecal enlargement	Pelvic nephrocalcinosis	Hypercalciuria	Reduced weight gain
Mannitol	+	+	+	+	+
Sorbitol	+	+	+	+	+
Xylitol	+	+	+	+	+
Isomalt	–	+	+	ND	+
Lactitol	+	+	+	+	+
Maltitol	+	?	+	+	+
Maltitol syrup[b]	–	+	ND	ND	+
Lactose	+	+	+	+	+

[a] + Positive effect, ? equivocal effect; – no effect; ND, no data.
[b] Formerly referred to as hydrogenated glucose syrup; includes products containing 90–98% maltitol.

and female volunteers consumed 70–100 g of xylitol per day for 2.0–5.3 years, no effects on urinary concentrations of calcium, catecholamines, magnesium, phosphate, bilirubin, serum amyloid P component or amino acids, nor on biochemical or haematological parameters related to the metabolism of lipids or carbohydrates, or energy were observed. A 32-month clinical study of cariogenicity in 157 children also failed to demonstrate any effect on hepatobiliary function when xylitol was consumed at doses of up to 20 g per day.

Metabolic studies. Polyols are passively and poorly absorbed, and considerable amounts may reach the lower digestive tract, where they are fermented by gut microflora, mainly to short-chain volatile fatty acids, which are absorbed and utilized. However, there are large differences in the rates of digestion and absorption of the various polyols and major differences in the degree of hepatic metabolism once they are absorbed. As a result, no common metabolic pathway has been identified that could explain a direct action on the adrenal medulla.

Differences between the rat and the human adrenal medulla. Since the Committee last evaluated the relevance to humans of the adrenal medullary lesions in rats, several studies have been published which may explain the species specificity of these lesions. Despite the general similarities of the anatomy of the adrenal medulla in rats and humans, several potentially important differences exist: (i) the rat adrenal medulla has two distinct chromaffin cell populations, one producing predominantly epinephrine and the other norepinephrine, while in humans there is no clear distinction between chromaffin cell types; (ii) the rat adrenal medulla also has a third cell type, namely the small granule-containing cell, the functions of which are largely unknown and for which there is no clearly defined human counterpart; and (iii) the peptide and protein composition of the secretory granules in the chromaffin cells differs between rats and humans.

A series of studies has shown that rat chromaffin cells are much more susceptible to mitogenic stimuli than human chromaffin cells, suggesting that rat chromaffin cells are inappropriate as a model to assess the potential effects of chemicals on human chromaffin cells. The high susceptibility of rat chromaffin cells to mitogenic (proliferative) stimuli may account, at least in part, for the higher rate of spontaneous phaeochromocytomas in rats (0.5% in Holtzman rats to 69% in Wistar rats) than in humans (0.005–0.1% reported in different studies). The chromaffin cells of mice, like those of humans, are resistant to mitogenic stimuli, and mice have a low spontaneous incidence of

adrenal medullary lesions (about 1%). Another important species difference is that, while many pharmacologically unrelated substances can induce phaeochromocytomas in rats, probably by enhancing the rate of spontaneous development, tumours of this type have not been reported to be associated with exposure to such substances in humans. A further difference between rats and humans is that the adrenal lesions reported in rats were not generally associated with increased catecholamine secretion or hypertension, whereas phaeochromocytomas in humans are often accompanied by hypertension.

A study was conducted in Wistar rats, which were fed diets containing 20% xylitol and either 0.4%, 0.2% or 0.05% calcium for up to 63 weeks. Controls received a diet containing 0.4% calcium, but no xylitol. Rats given 0.05% calcium in the diet showed lower urinary calcium levels and a significantly lower incidence of phaeochromocytomas than those in the groups given 0.4% and 0.2% calcium, although the total incidence of combined hyperplasia and neoplasia of the adrenal medulla was similar. In contrast, studies in humans conducted with sorbitol, lactitol, xylitol and maltitol syrup showed that these polyols either inhibited calcium absorption or did not affect urinary calcium levels.

Recent data support the hypothesis that altered calcium homeostasis is involved in the development of adrenal medullary proliferative lesions in long-term studies in rats. Administration of 20000 or 40000IU of vitamin D_3 daily to groups of six male Sprague–Dawley rats for 4 weeks resulted in dramatic increases in serum calcium concentrations and concomitant increases in the percentage of labelled chromaffin cells as measured by incorporation of 5-bromo-2′-deoxyuridine (broxuridine). Vitamin D_3 was not responsible for the increased rates of cell proliferation since it had no mitogenic effects on rat chromaffin cells *in vitro*. In similar experiments on xylitol and lactose, a slight, but significant, increase in the percentage of labelled chromaffin cells was found in the treated rats. These results and the fact that consumption of polyols by rats leads to hypercalciuria indicate that disturbed calcium homeostasis is possibly involved in the genesis of the adrenal medullary proliferative lesions observed in long-term studies of certain polyols or lactose in rats.

Conclusions. The Committee reviewed some recent literature dealing with the potential mechanisms for the production of phaeochromocytomas in rats fed high levels of polyols or lactose. It noted that functional differences have been identified between the adrenal medulla of the rat and that of other species, including humans, and

that ingestion of polyols or lactose was associated with increased calcium absorption in rats but not in humans, as inferred from hypercalciuria. While a reasonably clear association could be demonstrated between calcium absorption and the incidence of the adrenal medullary lesions, the actual mechanism whereby the increased absorption of calcium produces phaeochromocytomas in rats is still unknown, despite extensive research.

As noted at previous meetings of the Committee, the development of proliferative lesions of the adrenal medulla in rats fed polyols or lactose is associated only with high doses of these substances. Those compounds that have been tested do not induce these lesions in mice or dogs. Moreover, there is no indication that any of the polyols or lactose is metabolized to reactive intermediates, nor is there any evidence to suggest that any of these substances or their metabolites are genotoxic.

After reviewing the data cited above and noting certain unique features of the rat adrenal medulla, the Committee confirmed the view expressed at previous meetings that the occurrence of proliferative lesions of the adrenal medulla in rats fed polyols and lactose is a species-specific phenomenon and is not relevant to the toxicological evaluation of these substances for humans. The previous evaluations of polyols were maintained. No toxicological monograph was prepared.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *International harmonization of specifications*

In recognition of its advisory role to the Codex Committee on Food Additives and Contaminants in facilitating international trade and assuring a wholesome global food supply, the Committee noted the desirability and importance of harmonizing its specifications with those of other internationally recognized bodies, when possible. Specifications developed at the current meeting were considered in this light.

2.3.2 *Limits for arsenic, lead and heavy metals*

The Committee reaffirmed the intention expressed at its forty-fourth meeting (Annex 1, reference *116*) to consider lowering the existing general limits of 10 mg/kg for lead and 40 mg/kg for heavy metals for substances under consideration, unless data in support of these limits are provided. The Committee also reiterated its earlier recommendation that submissions on specifications should include actual

concentrations of lead and certain other heavy metals found in the substances under consideration. The Committee also agreed to continue, as decided at its forty-fourth meeting, to assess on a case-by-case basis the need for limits for arsenic in specifications for substances under review. Such limits would be reduced or withdrawn unless the information provided, the nature and source of the substance, or the levels of consumption indicate that limits for arsenic are necessary.

Finally, the Committee agreed that, for compounds with a limit of 10 mg/kg for heavy metals, no separate limit for lead would be set unless the information provided indicated that such a limit was necessary.

2.3.3 *Harmful analytical solvents and reagents*

The Committee noted the need to find alternative chemicals or methods of analysis that will help to eliminate the use of solvents or reagents that are known or suspected carcinogens or have undesirable effects on the environment. This requirement should be addressed when analytical methods are reviewed in connection with specifications as well as when the *Guide to specifications* (FAO Food and Nutrition Paper No. 5, Rev. 2) (Annex 1, reference *100*) is next revised.

2.3.4 *Cross-references*

The Committee agreed that specifications for methods for the identification and purity of compounds should not require cross-reference to other specifications. The Committee also re-emphasized that frequently used methods should be incorporated into FAO Food and Nutrition Paper No. 5, Rev. 2 (Annex 1, reference *100*).

2.3.5 *Flavouring agents*

For the first time, the Committee was asked to consider systematically a long list of flavouring agents. In view of the large number of such substances expected to be evaluated in the future, the Committee decided to tabulate the specifications for flavouring agents and not to use the standard specifications format. Specifications for compounds used as flavouring agents but also having other functions are listed both in the standard specifications format and in tabular form. Special methods of analysis, spectra for use in identification, and structural formulae will be included as appendices to the table of flavouring agents. Reference is made to FAO Food and Nutrition Paper No. 5, Rev. 2 (Annex 1, reference *100*), as appropriate.

Distillation ranges and limits for heavy metals, arsenic and non-volatile residues are not included in specifications for flavouring agents. For those which are also used in other ways, reference is made to the appropriate specifications monograph.

The Committee recognized that some of the common names used for commercial flavouring agents are ambiguous. In revising specifications for such agents, the Committee will employ, where it considers it appropriate, more systematic terminology. In order to avoid problems of communication, however, synonyms will be included in the specifications.

2.4 Principles governing intake assessments

The Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues (5) recognized that intake assessments of food additives, contaminants, and residues of pesticides and veterinary drugs should be considered an integral part of the risk assessment procedure for these substances. FAO and WHO had therefore decided to appoint several experts on intake assessment to the Joint FAO/WHO Expert Committee on Food Additives.

The Committee identified a number of issues that would require attention in the future in developing accurate models for assessing intake:

- provision of guidance on the collection of more accurate data on food consumption in future surveys;
- provision of guidance on the subdivision of regional diets according to staple foods;
- provision of guidance on the collection of more accurate data on concentrations of contaminants in foods; and
- evaluation of the quality of the available models for assessing food intake, including high food consumption.

A report on the Committee's deliberations was prepared, and it was decided that it should serve as a working paper at the next meeting of the Committee when food additives and contaminants are considered.

3. Specific food additives

The Committee re-evaluated several food additives considered at previous meetings. In addition, the Committee evaluated a large number of flavouring agents using the approach reviewed at its forty-

fourth meeting (Annex 1, reference *116*). Information on the evaluations and on specifications is summarized in Annex 2.

3.1 Antioxidants: gallates (dodecyl, octyl and propyl)

These substances were previously evaluated by the Committee at its third, sixth, eighth, tenth, fifteenth, sixteenth, seventeenth, twentieth, twenty-fourth, thirtieth and forty-first meetings (Annex 1, references *3*, *6*, *8*, *13*, *26*, *30*, *32*, *41*, *53*, *73* and *107*). At the twenty-fourth meeting, a group ADI of 0–0.2 mg per kg of body weight was established, based on the supposed similarity in biotransformation of these compounds. The gallates were again reviewed at the thirtieth meeting, when an ADI of 0–2.5 mg per kg of body weight was established for propyl gallate. However, the Committee was unable to establish an ADI for dodecyl and octyl gallate owing to lack of adequate data, and requested that studies be carried out on the metabolism of these substances, including identification of their metabolites in the milk of lactating animals and the toxicity of their known hydrolysis products.

At its forty-first meeting, the Committee reviewed new 4-week and 90-day toxicity studies in rats with propyl gallate and *in vitro* studies on the hydrolysis of the gallates in different tissues. The Committee allocated an ADI of 0–1.4 mg per kg of body weight for propyl gallate based on a NOEL of 1910 mg/kg in the feed (equal to 135 mg per kg of body weight per day) in a 90-day study in rats and a safety factor of 100. The Committee concluded that it was unlikely that either dodecyl or octyl gallate was carcinogenic or genotoxic; temporary ADIs were therefore allocated to both these substances, based on the NOELs observed in limited toxicological studies.

With octyl gallate, a slight hypochromic anaemia was observed at 100 mg per kg of body weight per day in a study in rats in which the substance was administered for two generations. A temporary ADI of 0–0.1 mg per kg of body weight was established for octyl gallate, based on a NOEL of 17.5 mg per kg of body weight per day in this study and a safety factor of 200.

With dodecyl gallate, a reduction in spleen weight and pathological changes in the liver, kidney and spleen were observed at 50 mg per kg of body weight per day in a 150-day study in rats in which the substance was administered by gavage. A temporary ADI of 0–0.05 mg per kg of body weight was established for dodecyl gallate, based on a NOEL of 10 mg per kg of body weight per day in this study and a safety factor of 200.

At its forty-first meeting, the Committee concluded that additional studies on the pharmacokinetics and metabolism of dodecyl, octyl and propyl gallate might help to explain the differences in toxicological potency of these compounds and requested data from such studies to be made available by 1996. If these studies did not satisfactorily resolve the issue with respect to the similarity of dodecyl and octyl gallate to propyl gallate, further toxicological studies (including long-term toxicity/carcinogenicity studies and genotoxicity studies) on dodecyl and octyl gallate might be required.

Since the forty-fourth meeting of the Committee, a few studies on gallates have been published; however, none of the data requested on the pharmacokinetics or metabolism of dodecyl, octyl and propyl gallate have been submitted.

The Committee therefore decided to retain the ADI for propyl gallate (0–1.4 mg per kg of body weight) established at the forty-first meeting, but did not extend the temporary ADIs for dodecyl and octyl gallate.

Since no new data on dodecyl, octyl and propyl gallates were submitted at the present meeting, a toxicological monograph was not prepared. The existing specifications for dodecyl, octyl and propyl gallate were revised, with minor changes.

3.2 Emulsifier: glycerol ester of wood rosin (ester gum)

This substance, which is used as a food additive in beverages and chewing gum, is prepared from wood rosin derived from the stumps of the longleaf pine (*Pinus palustris*) and purified to meet food-grade specifications. Wood rosin differs from tall oils and gums, which are derived from other parts of the tree. The resin acids in wood rosin can vary considerably in composition; however, the main resin acids in glycerol ester of wood rosin are the abietic acids (including dehydroabietic acid and neoabietic acid), the pimaric acids (including isopimaric acid and sandaracopimaric acid) and palustric acid. The carboxylic acid group of the resin acids of wood rosin is attached to a sterically hindered tertiary carbon, which is responsible for the resistance of the resin acid ester linkage to hydrolysis. Glycerol ester of wood rosin was previously considered by the Committee at its eighteenth, twentieth, thirty-third, thirty-seventh and forty-fourth meetings (Annex 1, references *35*, *41*, *83*, *94* and *116*).

At its twentieth meeting, the Committee, in the light of the strong ester bond and anticipated stability of this material, expressed the view that long-term and reproductive studies should be performed on

this specific substance, as opposed to unmodified resin, before further evaluation.

Specifications for the food-grade material were adopted at the thirty-seventh meeting of the Committee (Annex 1, references *94* and *96*). The specifications defined the material as a complex mixture of tri- and diglycerol esters of resin acids from wood rosin with a residual fraction of monoglycerol esters varying from 1% to 3%.

At its forty-fourth meeting, the Committee prepared a full toxicological monograph on glycerol ester of wood rosin (Annex 1, reference *117*). In addition, the Committee reviewed several studies on this substance, including a metabolic study in rats given unlabelled glycerol ester of wood rosin (identified as "beverage-grade ester gum") in the diet. The results of the metabolic study showed that glycerol ester of wood rosin was, for the most part, recovered unchanged from the faeces, which suggested that it was not hydrolysed in the gut to a significant extent and was largely unabsorbed. However, the lack of sensitivity of the analytical method used was such that a firm conclusion could not be reached as to the stability or non-bioavailability of this substance. The Committee was unable to establish an ADI and concluded that, as a minimum, studies demonstrating the metabolic stability and non-bioavailability of glycerol ester of wood rosin under conditions resembling those present in the human gastrointestinal tract would be required to permit further evaluation of this material.

At its present meeting, the Committee reviewed new studies with ^{14}C-labelled glycerol ester of wood rosin in rats and *in vitro*, which indicated that the food-grade material is quite stable in the gastrointestinal tract and that only a minor fraction, most probably the monoglycerol ester fraction, will undergo partial hydrolysis. The Committee also reviewed the toxicological studies that were available at the forty-fourth meeting, including 13-week toxicity studies in rats given food-grade and non-food-grade glycerol ester of wood rosin and a 2-year toxicity/carcinogenicity study in Sprague–Dawley rats given wood rosin (Annex 1, reference *117*). In the 13-week toxicity studies, the food-grade material was less toxic than the non-food-grade material. In the 2-year toxicity/carcinogenicity study, wood rosin did not induce any treatment-related histopathological effects when administered at dose levels of up to 434 mg per kg of body weight per day. The Committee concluded that glycerol ester of wood rosin is not genotoxic.

Although no long-term toxicity studies or reproductive toxicity studies were available for glycerol ester of wood rosin (as specified in

FAO Food and Nutrition Paper No. 52, Add. 3 (Annex 1, reference *118*)), the Committee considered that the data from previously reviewed studies and the new studies confirming non-bioavailability were adequate to establish an ADI. The Committee therefore allocated an ADI of 0–25 mg per kg of body weight to glycerol ester of wood rosin, based on the NOEL of 2500 mg per kg of body weight per day in the 13-week toxicity studies in rats with the food-grade material and a safety factor of 100. The Committee did not round the ADI to one significant figure (Annex 1, reference *116*, section 2.2.2), because this would have reduced the value by 20%.

An addendum to the toxicological monograph was prepared. The existing specifications were revised, with minor changes.

3.3 Flavouring agents

The Committee applied the modified safety evaluation procedure (see section 2.2.1) to the three groups of esters considered during the meeting. It first considered two components of the procedure that are common to all three structural classes of esters: the data on intake and hydrolysis.

Intake data

Intake estimates were derived from surveys in Europe and the USA. Estimates of the intake of flavouring agents by populations typically involve the acquisition of data on the amounts used in food. In the USA, a series of surveys was conducted between 1970 and 1987 by the National Academy of Sciences National Research Council (under contract to the Food and Drug Administration) in which information was obtained from ingredient manufacturers and food processors on the amount of each substance destined for addition to the food supply and on the usual and maximal levels at which each substance was added in a number of broad food categories (*6–9*). In Europe, a survey was conducted in 1995 by the International Organization of the Flavor Industry, in which flavour manufacturers reported the total amount of each flavouring agent incorporated into food sold in the European Union during the previous year (F. Grundschober, personal communication, 1996). Manufacturers were requested to exclude use of flavouring agents in pharmaceutical, tobacco or cosmetic products.

In using these survey data to estimate intakes of flavouring agents, it was assumed that only 60% of the total amount used is reported and that the total amount used in food is consumed by only 10% of the population.

$$\text{Intake (μg per person per day)} = \frac{\text{Annual volume of production (kg)} \times 10^9 \text{ (μg/kg)}}{\text{Population of consumers} \times 0.6 \times 365 \text{ days}}$$

The population of consumers was assumed to be 32×10^6 in Europe and 24×10^6 in the USA.

Data on hydrolysis

The ethyl, isoamyl and allyl esters considered at the present meeting are mostly simple structures, and data on representative compounds *in vivo* and *in vitro* indicate that they would be rapidly and completely hydrolysed after their ingestion as flavours. A wide range of enzymes (carboxyesterases and carboxylic acid hydrolases) is capable of hydrolysing esters into their constituent alcohols and acids. Carboxyesterases are found in many tissues, and there is high esterase activity in the intestinal tract, blood, liver, kidney, lung, brain and pancreas (*10–12*). Studies of a series of esters with straight-chain acid or alcohol moieties, in the range C1–C8, showed that purified esterases from rat and pig liver had different chain length requirements for optimal activity, but showed a trend for increased V_{max} (maximal rate of reaction) and pK_m (negative logarithm of Michaelis constant) values with an increase in the chain length of either the acid or the alcohol moiety (*10*, *12*). The multiplicity of esterases in some tissues and their wide tissue distribution result in the rapid hydrolysis of esters *in vivo* (*11*).

Data on the hydrolysis of flavour esters and selected structural analogues *in vitro* are summarized in Table 2. Hydrolysis of all esters was slow in artificial gastric juice (1–37% after 2 hours). In contrast, nearly all simple straight-chain saturated carboxylic acid esters were completely hydrolysed by artificial pancreatic juice within 2 hours. Branched-chain carboxylic acid esters and acetate esters were hydrolysed more slowly. The time to 50% hydrolysis ($T_{1/2}$) by pancreatic juice of those esters considered at the present meeting ranged from 2 minutes to over 3 hours. The data did not indicate that there would be a marked difference in the rate of hydrolysis between the three groups of esters, although some discrepancies were apparent: e.g. isoamyl isovalerate was hydrolysed more rapidly than the corresponding ethyl ester, but the reverse was true for isoamyl hexanoate.

The rates of hydrolysis of the esters by liver and intestinal tissue were about 1000 times those by artificial pancreatic juice, and the half-lives of the flavour esters considered at the meeting were 4 seconds or less. Ethyl isovalerate (not a flavouring agent) was hydrolysed more slowly, which suggested that branched-chain carboxylic acid

Table 2
Hydrolysis of flavour esters and selected analogues

Ester	Artificial gastric juice		Artificial pancreatic juice		Liver homogenate		Intestinal homogenate	
	% hydrolysis after 2h	$T_{1/2}$	% hydrolysis after 2h	$T_{1/2}$	% hydrolysis after 2h	$T_{1/2}$	% hydrolysis after 2h	$T_{1/2}$
Ethyl acetate	–	–	ND	–	–	–	100 (P)[a]	–
Ethyl butyrate	15[b]	8h10min[c]	100[b]	6min[c]	–	–	–	–
Ethyl isovalerate[d]	6[b]	23h10min[c]	34[b]	3h18min[c]	–	24s (R)[c]	–	2min13s (R)[c]
Ethyl hexanoate	–	4h53min[c]	–	3min[c]	–	0.1s (R)[c]	–	0.5s (R)[c]
Ethyl heptanoate	10[b]	12h50min[c]	100[b]	10min[c]	–	0.2s (R)[c]	–	0.6s (R)[c]
Ethyl nonanoate	37[b]	2h57min[c]	100[b]	6min[c]	–	–	–	–
Ethyl decanoate	–	–	80[a]	–	–	–	–	–
Ethyl dodecanoate	12[b]	10h40min[c]	100[b]	6min[c]	–	–	–	–
Ethyl cyclohexylpropanoate[d]	–	–	100[a]	–	–	–	–	–
Ethyl phenylacetate[d]	–	10h40min[c]	–	1h50min[c]	–	–	–	–
Ethyl furylpropanoate[d]	–	–	100[a]	–	–	–	–	–
Isoamyl acetate	–	–	20[a]	–	–	–	100 (P)[a]	–
Isoamyl butyrate	12[b]	11h[c]	100[b]	11min[c]	–	0.5s (R)[c]	–	0.1s (R)[c]
Isoamyl isovalerate	–	4h55min[c]	–	10min[c]	–	–	–	–
Isoamyl hexanoate	–	2h26min[c]	–	38min[c]	–	–	–	–
Isoamyl phenylacetate[d]	–	–	100[a]	–	–	–	–	–
Allyl hexanoate	–	18h40min[c]	100[a]	2min[c]	–	4s (R)[c]	–	0.1s (R)[c]
Allyl tiglate	–	–	ND[a]	–	–	–	100 (P)[a]	–
Allyl phenylacetate	–	–	100[a]	–	–	–	–	–
Related esters								
Butyl acetate	23[b]	5h18min[c]	72[b]	1h6min[c]	–	8min11s (R)[c]	–	1min48s (R)[c]
1,3-Dimethylbutyl acetate	–	–	15[a]	–	–	–	>99 (P)[a]	–
Benzyl acetate	–	–	50[a]	–	–	–	–	–
Methylanthrinilate	1[b]	99h10min[c]	ND,[a] 2[b]	69h10min[b]	>99 (P)[a]	26min40s (R)[c]	15 (P)[a]	2min28s (R)[c]

$T_{1/2}$, time to 50% hydrolysis; P, pig tissue; R, rat tissue; ND, not detected.
[a] Source: reference *13*.
[b] Source: reference *14*.
[c] Source: reference *15*.
[d] Close structural analogue of the flavouring agents considered at the meeting.

esters are hydrolysed more slowly than straight-chain carboxylic acid esters.

The data from the above-mentioned studies indicate that the ethyl, isoamyl and simpler allyl esters considered by the Committee would be completely metabolized on passage from the lumen of the gastrointestinal tract into the general circulation. The wide tissue distribution of esterase activity, which includes esterases in the blood, would ensure rapid hydrolysis of any intact ester that escaped first-pass metabolism in the intestine and liver. This conclusion was supported by data from an unpublished study in which isoamyl-3-(2′-furyl)propionate and allyl phenylacetate were not detected in the hepatic portal blood of guinea-pigs given an intraduodenal dose of these esters. Both esters underwent 98% hydrolysis in guinea-pig blood within 1 minute (*16*). Similarly, unhydrolysed ester was not detected in the blood of rats given benzyl acetate (see section 3.6.1). The data on hydrolysis indicate that allyl anthranilate may not undergo first-pass metabolism, and some of the intact ester may enter the general circulation. Measurable concentrations of methyl-*N*-methylanthranilate were present in the portal blood of guinea-pigs given an intraintestinal dose of this ester (*16*); however, the absorption of intact allyl anthranilate would not be of toxicological concern since slow hydrolysis would reduce the hepatotoxicity due to allyl alcohol (*17*).

3.3.1 *Ethyl esters*

Fifteen ethyl esters used as flavouring agents in food were evaluated by the safety evaluation procedure considered at the forty-fourth meeting (Annex 1, reference *116*) and modified at the present meeting (see Fig. 2). The esters evaluated were ethyl formate, ethyl acetate, ethyl propionate, ethyl butyrate, ethyl pentanoate (valerate), ethyl hexanoate (caproate), ethyl heptanoate (enanthate), ethyl octanoate (caprylate), ethyl nonanoate (pelargonate), ethyl decanoate (caprate), ethyl undecanoate, ethyl dodecanoate (laurate), ethyl tetradecanoate (myristate), ethyl hexadecanoate (palmitate), and ethyl octadecanoate (stearate). The ethyl esters considered are all straight-chain, saturated carboxylic acid esters and all occur as natural constituents of various foods. Ethyl formate, ethyl acetate, ethyl butyrate, ethyl heptanoate, ethyl nonanoate and ethyl dodecanoate have already been assigned ADIs, which are maintained.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, ethyl acetate, ethyl propionate and ethyl butyrate are the major ethyl esters to which humans are exposed, accounting for 91% and 97% respectively, of the

total annual volume of production of the 15 esters considered (*9*; F. Grundschober, unpublished data, 1996).

Application of the procedure to ethyl esters

In applying the modified procedure for flavouring substances (see Fig. 2) to an evaluation of the above-mentioned ethyl esters, the Committee assigned all 15 compounds to structural class I (step 1). These ethyl esters are considered to be completely hydrolysed in the human body to ethanol and their component carboxylic acids (see pp. 19–21), which are endogenous intermediates in human metabolism. Therefore, all the compounds were predicted to be metabolized to innocuous products (step 2), and the left-hand side of the decision tree was further considered. Apart from four compounds (ethyl acetate, ethyl propionate, ethyl butyrate and ethyl hexanoate), the intake estimates for all the ethyl esters were below the threshold for class I (1800 μg per day), so that they were considered not to be of safety concern, and no further information should be required (step 3(a)). For ethyl acetate, ethyl propionate, ethyl butyrate and ethyl hexanoate, it was then necessary to consider whether either the substance or any of its metabolites was endogenous (step 4(a)). In all four cases, the metabolites were known to occur endogenously, and therefore these compounds were considered to be of no safety concern at the estimated levels of current intake. Table 3 summarizes the evaluation of the 15 ethyl esters using the modified procedure.

Toxicity data

The ethyl esters evaluated were considered to be of no safety concern on the basis of structural class, the low estimated intakes and, where appropriate, their metabolism to endogenous substances. In consequence, no toxicity data were necessary for application of the procedure. Nevertheless, the Committee thought that it was useful to include the toxicity data on these substances (see Annex 3).

Group evaluation

In the unlikely event that all foods containing all of the 15 ethyl esters as flavouring substances were consumed simultaneously on a daily basis, the estimated daily intake for individuals in Europe and the USA would be 1000 and 870 μg per kg of body weight, respectively. The equivalent estimated daily per capita intakes of ethanol are 460 and 410 μg per kg of body weight, respectively. The endogenous synthesis of ethanol has been estimated to be approximately 40–80 mg per kg of body weight per day, which is of the order of 100–200 times

the estimated daily intake per kg of body weight derived from the ethyl esters.

Conclusion

The Committee concluded that the above-mentioned ethyl esters would not present safety concerns at the estimated levels of current intake. In all cases in which data on toxicity were available, they were compatible with this conclusion.

Toxicological monographs were not prepared. New specifications were prepared for ethyl propionate, ethyl pentanoate, ethyl hexanoate, ethyl octanoate, ethyl decanoate, ethyl undecanoate, ethyl tetradecanoate, ethyl hexadecanoate and ethyl octadecanoate. For ethyl undecanoate, the specifications were designated as "tentative". The existing specifications for ethyl formate, ethyl acetate, ethyl butyrate, ethyl heptanoate, ethyl nonanoate and ethyl dodecanoate were revised.

3.3.2 *Isoamyl alcohol and related esters*

Isoamyl alcohol and 10 of its related esters used as flavouring agents in food were evaluated by the safety evaluation procedure considered at the forty-fourth meeting (Annex 1, reference *116*) and modified at the present meeting (see Fig. 2). The esters evaluated were isoamyl formate, isoamyl acetate, isoamyl propionate, isoamyl butyrate, isoamyl hexanoate, isoamyl octanoate, isoamyl nonanoate, isoamyl isobutyrate, isoamyl isovalerate and 3-methylbutyl 2-methylbutyrate. Seven of these esters are linear saturated carboxylic acid esters and three are branched-chain carboxylic acid esters.

Isoamyl alcohol used for flavouring purposes is a mixture of 3-methyl-1-butanol (isoamyl alcohol) (about 80%) and 2-methyl-1-butanol (about 20%). Isoamyl acetate and isoamyl butyrate were evaluated by the Committee at its twenty-third meeting, when a group ADI for isoamyl butyrate of 0–3 mg per kg of body weight expressed as isoamyl alcohol was allocated (Annex 1, reference *50*). Since studies on isoamyl acetate indicated that it would be hydrolysed *in vivo* similarly to isoamyl butyrate, the Committee decided to include it in the group ADI for isoamyl butyrate. At its present meeting, the Committee decided to maintain this ADI.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, isoamyl acetate is by far the most important isoamyl ester to which humans are exposed, accounting for 79% and 69%, respectively, of the total annual volume of

Table 3
Summary of the results of safety evaluations of 15 ethyl esters[a]

Substance	*Step 3 (a)* Does intake exceed the threshold for human intake?	*Step 4 (a)* Metabolized to endogenous substances?	Products of hydrolysis	Metabolic fate	Conclusion based on current intake
Ethyl formate	No Europe: 1400 USA: 500	NR	Ethanol and formic acid	Metabolized in recognized biochemical pathways	No safety concern
Ethyl acetate	Yes Europe: 28000 USA: 28000	Yes	Ethanol and acetic acid	Endogenous in humans	
Ethyl propionate	Yes Europe: 3900 USA: 5900	Yes	Ethanol and propionic acid	Endogenous in humans	
Ethyl butyrate	Yes Europe: 24000 USA: 16000	Yes	Ethanol and butyric acid	Endogenous in humans	
Ethyl pentanoate	No Europe: 200 USA: 72	NR	Ethanol and valeric acid	Metabolized in recognized biochemical pathways	

Ethyl hexanoate	Yes Europe: 2200 USA: 600	Yes	Ethanol and hexanoic acid	Endogenous in humans	No safety concern
Ethyl heptanoate	No Europe: 220 USA: 190	NR	Ethanol and heptanoic acid	Metabolized in recognized biochemical pathways	
Ethyl octanoate	No Europe: 450 USA: 38	NR	Ethanol and octanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl nonanoate	No Europe: 140 USA: 47	NR	Ethanol and nonanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl decanoate	No Europe: 180 USA: 55	NR	Ethanol and decanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl undecanoate	No Europe: 30 USA: 0.17	NR	Ethanol and undecanoic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl dodecanoate	No Europe: 240 USA: 45	NR	Ethanol and lauric acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl tetradecanoate	No Europe: 250 USA: 180	NR	Ethanol and myristic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl hexadecanoate	No Europe: 88 USA: 1.3	NR	Ethanol and palmitic acid	Metabolized in glycolytic and fatty acid pathways	
Ethyl octadecanoate	No Europe: 2.6 USA: 0.38	NR	Ethanol and octadecanoic acid	Metabolized in glycolytic and fatty acid pathways	

NR, not required for evaluation because consumption of the substance was determined to be of no safety concern at an earlier step of the procedure.

[a] *Step 1*: All of the esters in this group are in structural class I, the human intake threshold of which is 1800 µg per day.
Step 2: All of the esters in this group are hydrolysed to their component alcohol, ethanol, and their corresponding carboxylic acids, all of which are innocuous products.
Intake values are expressed in µg per day.

production of the 10 esters considered (*9*; F. Grundschober, personal communication, 1996). The intake of isoamyl butyrate, isoamyl alcohol and isoamyl isovalerate is approximately 20% of that of isoamyl acetate. The other esters are produced in much smaller quantities. With the exception of isoamyl nonanoate, isoamyl alcohol and all of the above-mentioned esters have been detected as natural constituents of various foods and alcoholic beverages.

Application of the procedure to isoamyl alcohol and related esters

In applying the modified procedure for flavouring agents (Fig. 2) to an evaluation of isoamyl alcohol and its related esters, the Committee assigned all 11 compounds to class I of the three structural classes (step 1). These esters are considered to be completely hydrolysed in the human body to isoamyl alcohol and its component carboxylic acids (see pp. 19–21), and the hydrolysis products either occur as, or are rapidly metabolized to, normal endogenous intermediates in human metabolism of amino acids and fatty acids. Since all 11 compounds were predicted to be metabolized to innocuous products (step 2), the left-hand side of the decision tree was further considered. Apart from two compounds (isoamyl acetate and isoamyl butyrate), the intake estimates for isoamyl alcohol and its related esters were below the threshold for class I (1800 μg per day), so that they were considered not to be of safety concern, and no further information should be required (step 3(a)). For isoamyl acetate and isoamyl butyrate, it was then necessary to consider whether the substance or any of its metabolites was endogenous (step 4(a)). In both cases, the metabolites were known to occur endogenously, and therefore these compounds were considered to be of no safety concern at the estimated levels of current intake.

2-Methyl-1-butanol, one of the components of isoamyl alcohol, was also evaluated using the modified procedure. This compound belongs to class I of the three structural classes. It is metabolized to innocuous products, and its intake does not exceed the threshold for class I. The Committee therefore considered this substance not to be of safety concern, and did not require any additional information.

Table 4 summarizes the evaluation of isoamyl alcohol and its related esters by the modified procedure.

Toxicity data

The isoamyl esters evaluated were considered to be of no safety concern on the basis of structural class, the low estimated intakes and, where appropriate, their metabolism to endogenous substances. In consequence, no toxicity data were necessary for application of the

Table 4
Summary of the results of safety evaluations of isoamyl alcohol and 10 isoamyl esters[a]

Substance	*Step 3 (a)* Does intake exceed the threshold for human intake?	*Step 4 (a)* Metabolized to endogenous substances?	Products of hydrolysis and primary alcohol oxidation	Metabolic fate	Conclusion based on current intake
Isoamyl alcohol	No Europe: ND USA: 1600	NR	Isovaleric acid	Oxidation product. Metabolized in amino acid and fatty acid pathways	No safety concern
Isoamyl formate	No Europe: 50 USA: 30	NR	Isovaleric acid and formic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl acetate	Yes Europe: 23000 USA: 10000	Yes	Isovaleric acid and acetic acid	Endogenous in humans	
Isoamyl propionate	No Europe: 300 USA: 120	NR	Isovaleric acid and propionic acid	Metabolized in amino acid, fatty acid and tetrahydrofolate pathways	
Isoamyl butyrate	Yes Europe: 4000 USA: 1900	Yes	Isovaleric acid and butyric acid	Endogenous in humans	
Isoamyl hexanoate	No Europe: 90 USA: 30	NR	Isovaleric acid and hexanoic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl octanoate	No Europe: 20 USA: 0.6	NR	Isovaleric acid and octanoic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl nonanoate	No Europe: 2 USA: 0.001	NR	Isovaleric acid and nonanoic acid	Metabolized in amino acid and fatty acid pathways	
Isoamyl isobutyrate	No Europe: 12 USA: 7	NR	Isovaleric acid and isobutyric acid	Metabolized in amino acid and fatty acid pathways.	
Isoamyl isovalerate	No Europe: 1400 USA: 800	NR	Isovaleric acid	Primary component of hydrolysis. Metabolized in amino acid and fatty acid pathways	
Isoamyl 2-methylbutyrate	No Europe: 6.5 USA: 2.1	NR	Isovaleric acid and 2-methylbutyric acid	Metabolized in amino acid and fatty acid pathways	

NR, not required for evaluation because consumption of the substance was determined to be of no safety concern at an earlier step of the procedure; ND, no intake data reported.
[a] *Step 1:* All of the esters in this group are in structural class I, the human intake threshold of which is 1800 µg per day.
Step 2: All of the esters in this group are hydrolysed to their component alcohols and the corresponding carboxylic acids, all of which are innocuous products.
Intake values are expressed in µg per day.

procedure. Nevertheless, the Committee thought that it was useful to include the toxicity data on these substances (see Annex 3).

Group evaluation

In the unlikely event that all foods containing isoamyl alcohol and its 10 related esters as flavouring agents were consumed simultaneously on a daily basis, the estimated daily per capita consumption in Europe and the USA would be 670 and 240 μg per kg of body weight, respectively. The equivalent estimated daily per capita intakes of isoamyl alcohol would be 340 and 170 μg per kg of body weight, respectively, well below the ADI of 0–3 mg per kg of body weight established for isoamyl alcohol as a component of isoamyl acetate and isoamyl butyrate.

Conclusion

The Committee concluded that isoamyl alcohol and the above-mentioned related esters do not present safety concerns at the estimated current levels of intake. In all cases in which toxicity data were available, they were compatible with this conclusion.

Toxicological monographs were not prepared. New specifications were prepared for isoamyl alcohol, isoamyl formate, isoamyl propionate, isoamyl hexanoate, isoamyl octanoate, isoamyl nonanoate, isoamyl isobutyrate, isoamyl isovalerate and isoamyl 2-methylbutyrate. For isoamyl octanoate, isoamyl nonanoate and isoamyl 2-methylbutyrate, the specifications were designated as "tentative". The existing specifications for isoamyl acetate and isoamyl butyrate were revised.

3.3.3 *Allyl esters*

Twenty-one allyl esters used as flavouring agents in food were evaluated by the procedure considered at the forty-fourth meeting (Annex 1, reference *116*) and modified at the present meeting of the Committee (see Fig. 2). As a consequence of the Committee's decision not to consider step 7 of the original proposed procedure (Fig. 1) at this meeting, allyl 2-furoate could not be evaluated beyond step 6. The esters evaluated were allyl propionate, allyl butyrate, allyl hexanoate, allyl heptanoate, allyl octanoate, allyl nonanoate, allyl isovalerate, allyl sorbate, allyl 10-undecenoate, allyl tiglate, allyl 2-ethylbutyrate, allyl cyclohexaneacetate, allyl cyclohexanepropionate, allyl cyclohexanebutyrate, allyl cyclohexanevalerate, allyl cyclohexanehexanoate, allyl phenylacetate, allyl phenoxyacetate, allyl cinnamate, allyl anthranilate and allyl 2-furoate. These esters are formed from

allyl alcohol and carboxylic acids. Of the 21 allyl esters, only allyl hexanoate and allyl 2-furoate have been reported as natural components of food.

Allyl hexanoate, allyl heptanoate and allyl isovalerate were evaluated by the Committee at its thirty-seventh meeting (Annex 1, reference *94*). In view of evidence that these esters are all rapidly hydrolysed to allyl alcohol, the Committee concluded that they should be evaluated for a group ADI on the basis of the allyl alcohol moiety. The Committee allocated an ADI of 0–0.05 mg per kg of body weight for allyl hexanoate, allyl heptanoate and allyl isovalerate as allyl alcohol equivalent. This corresponds to 0–0.13 mg per kg of body weight for allyl hexanoate, 0–0.15 mg per kg of body weight for allyl heptanoate, or 0–0.12 mg per kg of body weight for allyl isovalerate, or *pro rata* combinations of these substances. These ADIs were maintained at the present meeting.

The Committee concluded, on the basis of the toxicological data available, that there were no existing unresolved toxicity problems in relation to allyl alcohol. Thus, in agreement with the general considerations dealing with the application of the procedure, it could be applied to the allyl esters. None of the other allyl esters have previously been evaluated by the Committee.

According to production statistics and derived estimated intakes of flavouring agents in Europe and the USA, allyl hexanoate, allyl heptanoate and allyl cyclohexanepropionate are the major allyl esters to which humans are exposed (*9*; F. Grundschober, personal communication, 1996). These three esters account for over 96% (approximately 85%, 4% and 7%, respectively) of the total annual volume of production in Europe of the 21 allyl esters considered and for over 99% (approximately 85%, 3% and 12%, respectively) of the total annual volume of production in the USA. The other esters are produced in much smaller quantities. The estimated daily per capita intake of allyl hexanoate, the allyl ester produced in by far the greatest annual volume, is 43 µg per kg of body weight per day in Europe and 14 µg per kg of body weight per day in the USA.

Application of the procedure to allyl esters

In applying the modified procedure for flavouring agents (see Fig. 2) to an evaluation of the 21 allyl esters considered at the present meeting, the Committee assigned all except three of the compounds to class II of the three structural classes (step 1). Allyl phenoxyacetate, allyl anthranilate and allyl 2-furoate were assigned to class III.

Generally, allyl esters would be expected to be hydrolysed in the human body to allyl alcohol and their corresponding carboxylic acids (see pp. 19–21). However, none of the allyl esters considered could be predicted to be metabolized to innocuous products (step 2), since all 21 would be hydrolysed to allyl alcohol. Accordingly, the right-hand side of the decision tree was considered. For all 21 allyl esters except allyl hexanoate, the intake estimate was below the threshold for the structural class for the substance (540 μg per day for class II and 90 μg per day for class III). For allyl hexanoate, the intake estimates in Europe (2600 μg per day) and the USA (820 μg per day) both exceeded the threshold for class II. Accordingly, additional data on this substance or a closely related substance were required in order to proceed with the safety evaluation (step 3(b)). For the remaining 20 substances, it was then necessary to determine whether adequate data were available on the substance or on a structurally related substance that provide an adequate margin of safety at current estimated levels of intake (step 4(b)). This condition was met for all the 20 esters evaluated, except allyl 2-furoate.

Table 5 summarizes the evaluation of the 21 allyl esters using the modified procedure.

Toxicity data

Allyl alcohol. Results of dietary studies in animals indicate that allyl alcohol and allyl esters may cause liver damage. The mechanism of hepatotoxicity involves acrolein, an oxidation product of allyl alcohol, which is known to damage the periportal region of the liver lobule (*29*).

The current intake of allyl alcohol from the hydrolysis of all of the allyl esters was evaluated in relation to the ADI for allyl alcohol of 0–0.05 mg per kg of body weight allocated by the Committee at its thirty-seventh meeting (Annex 1, reference *94*). This ADI is based on a NOEL of 4.8–6.2 mg per kg of body weight per day from a 15-week study in rats given allyl alcohol in drinking-water (*30*). In addition, the Committee considered another study which had not previously been evaluated in which drinking-water containing 300 mg/l of allyl alcohol was administered to rats for 106 weeks. The results did not raise any additional concerns (*31*).

Allyl propionate. The results of a 13-week study in which allyl propionate was fed to rats in the diet at a dose level of 18 mg per kg of body weight per day did not reveal any evidence of hepatotoxicity (*18*).

Allyl butyrate. No signs of liver toxicity were noted when allyl butyrate was administered by gavage to rats at a dose of 50 mg per kg of

body weight per day for 17 weeks. However, there was slight to marked peribronchial lymphocytic infiltration of the lungs, which was also observed in control animals but to a lesser degree (*20*). Peribronchial lymphocytic infiltration of the lungs was the only effect reported in a second 17-week study in which rats were given allyl butyrate by gavage at a dose of 50 mg per kg of body weight per day (*19*).

Allyl hexanoate. In short-term studies in rats, administration of allyl hexanoate at a dose of 50 mg per kg of body weight per day was not associated with any evidence of hepatotoxicity (*19*, *20*).

No adverse effects were reported when allyl hexanoate was incorporated into the diet of rats at a dose of 125 mg per kg of body weight per day for 1 year (*20*). Adjustment of the dose to take into account the loss of allyl hexanoate from the diet due to evaporation (approximately 31% per week) resulted in an estimated intake of 86 mg per kg of body weight per day.

Allyl heptanoate. In dietary studies of 13 weeks' duration in rats and of 18 months' duration in dogs, no adverse effects were observed at doses of up to 500 and 25 mg per kg of body weight per day, respectively (*18*, *21*).

Allyl octanoate. No short-term studies were available on allyl octanoate. However, the structure of this compound is closely related to that of allyl hexanoate.

Allyl nonanoate. No short-term studies were available on allyl nonanoate. However, the structure of this compound is closely related to that of allyl heptanoate.

Allyl isovalerate. No evidence of hepatotoxicity was observed at daily intake levels of 62 mg per kg of body weight in short- and long-term studies in mice and rats (*22*).

Allyl sorbate. No short-term studies were available on allyl sorbate. However, this compound is structurally related to allyl hexanoate. Sorbic acid was evaluated by the Committee at its seventeenth meeting (Annex 1, reference *32*), when an ADI of 0–25 mg per kg of body weight was established. No adverse effects were reported when rats and mice were maintained on diets containing 1.5% sorbic acid for 2 years and 80 weeks, respectively (*23*, *24*).

Allyl 10-undecenoate. No short-term studies were available on allyl 10-undecenoate. However, this compound is structurally related to allyl heptanoate. No adverse effects were reported in adult rats or their offspring when the hydrolysis product, 10-undecenoic acid, was administered by gavage at 100, 200 or 400 mg per kg of body weight

Table 5
Summary of the results of safety evaluations of 21 allyl esters

Substance	*Step 1* Structural class	*Step 2*[a] Metabolized to innocuous products?	*Step 3 (b)*[b] Does intake exceed the threshold for human intake?	*Step 4 (b)* Adequate NOEL for substance or related substance?	Toxicological data	Conclusion based on current intake
Allyl propionate	II	No	No Europe: 7.9 USA: <0.01	Yes	NOELs for allyl alcohol and propionic acid provide an adequate margin of safety for allyl alcohol and propionic acid from the hydrolysis of allyl propionate (Annex 1, reference *94*) (*18*)	No safety concern
Allyl butyrate	II	No	No Europe: 11 USA: <0.01	Yes	NOELs for allyl alcohol and allyl butyrate provide an adequate margin of safety for allyl butyrate (Annex 1, reference *94*) (*19*)	
Allyl hexanoate[c]	II	No	Yes Europe: 2600 USA: 820	–	NOELs for allyl alcohol and allyl hexanoate provide an adequate margin of safety for allyl hexanoate; ADI for allyl hexanoate, 0–0.13 mg per kg of body weight (Annex 1, reference *94*) (*20*)	
Allyl heptanoate	II	No	No Europe: 130 USA: 28	Yes	NOELs for allyl alcohol and allyl heptanoate provide an adequate margin of safety for allyl heptanoate; ADI for allyl heptanoate, 0–0.15 mg per kg of body weight (Annex 1, reference *94*) (*18*, *21*)	
Allyl octanoate	II	No	No Europe: 45 USA: 1.3	Yes	NOELs for allyl alcohol and allyl hexanoate provide an adequate margin of safety for allyl octanoate (Annex 1, reference *94*) (*21*)	

Allyl nonanoate	II	No	No Europe: 2.4 USA: <0.01	Yes	NOELs for allyl alcohol and allyl heptanoate provide an adequate margin of safety for allyl nonanoate (Annex 1, reference *94*) (*21*)	No safety concern
Allyl isovalerate	II	No	No Europe: <0.01 USA: 0.19	Yes	NOELs for allyl alcohol and allyl isovalerate provide an adequate margin of safety for allyl isovalerate; ADI for allyl isovalerate, 0–0.12 mg per kg of body weight (Annex 1, reference *94*) (*22*)	
Allyl sorbate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol, sorbic acid and allyl hexanoate provide an adequate margin of safety for the hydrolysis products of allyl sorbate; ADI for sorbic acid, 0–25 mg per kg of body weight (Annex 1, reference *32*) (*23*, *24*)	
Allyl 10-undecenoate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol and 10-undecenoic acid provide an adequate margin of safety for the hydrolysis products of allyl 10-undecenoate (Annex 1, reference *94*) (*25*)	
Allyl tiglate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol and for a structurally related analogue, 3-methyl-2-butenoic acid, provide an adequate margin of safety for the hydrolysis products of allyl tiglate (Annex 1, reference *94*) (*26*)	
Allyl 2-ethylbutyrate	II	No	No Europe: <0.01 USA: 0.02	Yes	NOELs for allyl alcohol and 2-ethylbutyric acid provide an adequate margin of safety for the hydrolysis products of allyl 2-ethylbutyrate (Annex 1, reference *94*) (*27*)	

Table 5 (*continued*)

Substance	*Step 1* Structural class	*Step 2*[a] Metabolized to innocuous products?	*Step 3 (b)*[b] Does intake exceed the threshold for human intake?	*Step 4 (b)* Adequate NOEL for substance or related substance?	Toxicological data	Conclusion based on current intake
Allyl cyclohexaneacetate	II	No	No Europe: <0.01 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester, allyl cyclohexanepropionate, provide an adequate margin of safety for allyl cyclohexaneacetate (Annex 1, reference *94*) (*19*, *20*)	No safety concern
Allyl cyclohexanepropionate	II	No	No Europe: 220 USA: 110	Yes	NOELs for allyl alcohol and allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanepropionate (Annex 1, reference *94*) (*19*, *20*; H.A. Shelanski, personal communication, 1953; H. Paynter, personal communication, 1957)	
Allyl cyclohexanebutyrate	II	No	No Europe: 0.14 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanebutyrate (Annex 1, reference *94*) (*19*, *20*)	
Allyl cyclohexanevalerate	II	No	No Europe: 0.14 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanevalerate (Annex 1, reference *94*) (*19*, *20*)	
Allyl cyclohexanehexanoate	II	No	No Europe: 0.36 USA: <0.01	Yes	NOELs for allyl alcohol and for the structurally related ester allyl cyclohexanepropionate provide an adequate margin of safety for allyl cyclohexanehexanoate (Annex 1, reference *94*) (*19*, *20*)	

Allyl phenylacetate	II	No	No Europe: 7.5 USA: <0.01	Yes	NOELs for allyl alcohol and for the phenylethyl ester of the hydrolysis product phenylacetic acid provide an adequate margin of safety for the hydrolysis products of allyl phenylacetate (Annex 1, reference *94*) (*20*)	No safety concern
Allyl phenoxyacetate	III	No	No Europe: 35 USA: 2.5	Yes	NOELs for allyl alcohol and for the structurally related ethyl ester of *p*-methylphenoxy-acetic acid provide an adequate margin of safety for the hydrolysis products of allyl phenoxyacetate (Annex 1, reference *94*) (*28*)	
Allyl cinnamate	II	No	No Europe: 5.4 USA: 0.28	Yes	NOELs for allyl alcohol and for cinnamaldehyde, the aldehyde precursor of cinnamic acid, provide an adequate margin of safety for the hydrolysis products of allyl cinnamate (Annex 1, reference *94*) (Trubeck Laboratories, unpublished data, 1958)	
Allyl anthranilate	III	No	No Europe: 0.14 USA: 0.09	Yes	NOELs for allyl alcohol and for methylanthranilate, a simple ester of anthranilic acid, provide an adequate margin of safety for the hydrolysis products of allyl anthranilate (Annex 1, reference *94*) (*20*)	
Allyl 2-furoate[d]	III	No	No Europe: 0.14 USA: <0.01	No	–	–

[a] All allyl esters are metabolized to allyl alcohol and their respective carboxylic acids.
[b] The thresholds for human intake for classes II and III are 540 µg per day and 90 µg per day, respectively. All intake values are expressed in µg per day.
[c] As evaluation of allyl hexanoate resulted in a positive response to the question in step 3(b) of Fig. 2, this flavouring agent was evaluated individually, on the basis of the available toxicity data.
[d] Evaluation of allyl 2-furoate was postponed, pending consideration of step 4(b) of the original proposed procedure (Annex 1, reference *116*) by the Committee (see Fig. 1).

per day for up to 9 months (*25*). Similarly, no adverse effects were reported in mice given this compound by gavage at 100, 200 or 400 mg per kg of body weight per day for 6 months (*25*).

Allyl tiglate. No short-term studies were available on allyl tiglate. However, this compound is structurally related to allyl isovalerate. In a limited study of the hepatotoxicity of the metabolites of isoprene derivatives, groups of rats were given the isomeric acid, 3-methyl-2-butenoic acid, by gavage at doses of 400–2500 mg per kg of body weight per day for 1–2 months (*26*). The study, which was limited to cytological examination of the liver, revealed no abnormalities.

Allyl 2-ethylbutyrate. No short-term studies were available on allyl 2-ethylbutyrate. In a limited study, no effects were reported when a diet containing 0.6% 2-ethylbutyric acid (equivalent to 300 mg per kg of body weight per day) was fed to rats for 90 days (*27*).

Allyl cyclohexanepropionate. No adverse effects were reported in rats given diets containing allyl cyclohexanepropionate at a dose equivalent to 50 or 125 mg per kg of body weight per day for 27–28 weeks or 1 year, respectively (*19*, *20*). Similarly, no adverse effects were observed when rats were given 2, 20 or 100 mg per kg of body weight of allyl cyclohexanepropionate in sesame oil by stomach tube daily, 5 days per week, for 3 months (H.A. Shelanski, personal communication, 1953) or were maintained on diets containing 0.1% or 0.25% allyl cyclohexanepropionate for 13 weeks (H. Paynter, personal communication, 1957).

Allyl cyclohexaneacetate, allyl cyclohexanebutyrate, allyl cyclohexanevalerate and allyl cyclohexanehexanoate. No short-term studies on these esters were available. However, they are all structurally related to allyl cyclohexanepropionate.

Allyl phenylacetate. No short-term studies were available. No adverse effects were observed when rats were maintained on diets providing 500 mg per kg of body weight per day of the structurally related phenyl ester of phenylacetic acid, phenylethyl phenylacetate, for 17 weeks (*20*).

Allyl phenoxyacetate. No short-term studies were available. No adverse effects were observed when rats were maintained on diets providing 15 mg per kg of body weight per day of the structurally related ethyl ester of *p*-methylphenoxyacetic acid for 90 days (*28*).

Allyl cinnamate. No short-term studies were available. Cinnamaldehyde, the aldehyde precursor of cinnamic acid, was studied in rats, which were maintained on diets providing 50, 125 or 500 mg of

cinnamaldehyde per kg of body weight per day for 16 weeks. At 500 mg per kg of body weight per day, slight hepatocellular swelling and hyperkeratosis of the gastric squamous epithelium were reported (*20*). No adverse effects were reported when cinnamaldehyde was added to the diet of rats to provide an average daily intake of up to 227 mg per kg of body weight for 12 weeks (Trubeck Laboratories, unpublished data, 1958).

Allyl anthranilate. No short-term studies were available. No adverse effects were reported when rats were maintained for 90 days on diets providing 50 or 500 mg per kg of body weight per day of methyl anthranilate, a simple ester of anthranilic acid (*20*).

Allyl 2-furoate. No data on the ester or on a closely related substance were available to enable the Committee to conclude that there was an adequate margin of safety for this flavouring substance (see Fig. 2, step 4(b)). In addition, no data on the hydrolysis of allyl-2-furoate were available. The Committee therefore requested additional toxicity data on this substance.

Group evaluation

Neither the estimated daily per capita intake of allyl hexanoate in Europe (43 µg per kg of body weight per day) nor that in the USA (14 µg per kg of body weight per day) exceeds the ADI allocated by the Committee. Similarly, the estimated current intakes of allyl heptanoate and allyl isovalerate are below the individual ADIs previously allocated by the Committee. For the other allyl esters considered at the meeting (except allyl 2-furoate), a NOEL exists for the substance itself or for a structurally related substance that provides an adequate margin of safety at the estimated current levels of intake. In addition, the estimated current intake of allyl alcohol from the consumption of all 21 allyl esters is 18 µg per kg of body weight per day in Europe and 5.8 µg per kg of body weight per day in the USA. These estimates are below the ADI of 0–0.05 mg per kg of body weight previously established for allyl alcohol.

Conclusions

Evaluation of this group of esters demonstrated that the safety evaluation procedure is capable of identifying flavouring substances of possible safety concern at the estimated current levels of intake, such as allyl hexanoate. The Committee noted that this concern was met by its previous evaluation of allyl hexanoate (together with allyl heptanoate and allyl isovalerate) (Annex 1, reference *94*). The Committee concluded that these allyl ester flavouring agents do not

present safety concerns at the estimated current levels of intake. Whenever data on toxicity were available, they were compatible with this conclusion.

Evaluation of allyl 2-furoate was postponed, pending consideration of either additional toxicity data or step 5(b) of the original procedure (Fig. 1) by the Committee at a future meeting.

Toxicological monographs were not prepared. New tentative specifications were prepared for allyl propionate, allyl sorbate, allyl cyclohexaneacetate, allyl cyclohexanebutyrate, allyl cyclohexanevalerate, allyl cyclohexanehexanoate, allyl phenylacetate, allyl cinnamate, allyl anthranilate and allyl 2-furoate. New specifications were also prepared for allyl butyrate, allyl octanoate, allyl nonanoate, allyl 10-undecanoate, allyl 2-ethylbutyrate and allyl phenoxyacetate. The existing specifications for allyl hexanoate, allyl heptanoate, allyl isovalerate, allyl tiglate and allyl cyclohexanepropionate were revised.

3.4 Sweetening agent: alitame

Alitame was last considered at the forty-fourth meeting of the Committee (Annex 1, reference *116*), but no ADI was allocated because of significant concerns about deficiencies in the carcinogenicity studies in rats. Specifically, in a study in Long–Evans rats, poor survival rates at 24 months and an increased incidence of hepatocellular adenomas in females at the highest dose were noted. While it was considered unlikely that these adenomas would progress to hepatocellular carcinomas, the data were considered inconclusive in this regard. The second study, in Sprague–Dawley rats, showed lower survival rates at both 22 and 24 months than those found in the Long–Evans rats, and hence was considered inadequate to provide further information regarding the potential carcinogenicity of alitame.

At its present meeting, the Committee reconsidered the question of the adequacy of the carcinogenicity studies in the light of the survival rates of animals in contemporary long-term studies (see section 2.2.2) and a further statistical analysis of the data from the two studies, which specifically assessed the adequacy of the study in Sprague–Dawley rats to detect liver lesions.

The Committee noted that, while the survival rate of Long–Evans rats at 24 months was low, it was comparable to that observed in contemporary studies in rats of this strain. No hepatocellular carcinomas were observed in the study in Long–Evans rats. It also noted that the survival rate of Sprague–Dawley rats was comparable to that in contemporary studies in rats of this strain and that because there were

more animals per group initially than in the study using Long–Evans rats, the number of surviving animals was comparable between the two strains. On the basis of a logistical regression model developed using data from the study with Long–Evans rats, an increased probability of developing hepatocellular adenomas and eosinophilic foci would have been expected in the Sprague–Dawley rats, given the dose levels and the duration of the study, but no such increase was observed. On the basis of these considerations, the two studies were considered adequate to assess the potential carcinogenicity of alitame.

The Committee concluded that there was no evidence that alitame was carcinogenic, and therefore allocated an ADI of 0–1 mg per kg of body weight, based on the NOEL of 100 mg per kg of body weight identified at the forty-fourth meeting in the 18-month study in dogs and a safety factor of 100.

Although the Committee had not specifically requested a further study of tolerance to repeated doses of alitame in diabetic subjects, it was aware that such a study is under way, and requested that the results be submitted for evaluation when available.

An addendum to the toxicological monograph was prepared. The existing specifications were revised, with minor changes.

3.5 Thickening agent: konjac flour

Konjac flour was previously considered by the Committee at its forty-first meeting (Annex 1, reference *107*). At that meeting, the Committee allocated a temporary ADI "not specified" on the basis of the available toxicological data, particularly data from human studies, the long history of use of konjac flour as a food in China and Japan, and estimates of consumption from traditional and anticipated food additive uses. The results of additional short-term toxicity studies, which the Committee was informed had been conducted in rats and dogs, together with adequate data on the fate of konjac flour in the gut and information on its influence on the bioavailability of fat-soluble vitamins, were requested for review by 1996.

No information on the short-term toxicity studies referred to in the forty-first report could be located by the Committee at its present meeting. The Committee reviewed data from additional short-term studies and a long-term study, all conducted in rats. The short-term studies were a 28-day study on the effect of konjac flour on protein digestion and absorption, and a 12-week study on the hypocholesterolaemic effect of konjac flour. The long-term study was on the effect of konjac flour on calcium and phosphorus metabolism

and tissue pathology. While these studies were not specifically designed to assess the potential toxicity of konjac flour, no evidence of toxicity was reported at a dose of 10% in the diet for up to 12 weeks, or at 1% in the diet for 18 months. Two additional studies on genotoxicity provided no evidence of potential to induce forward mutations at the thymidine kinase locus in lymphoma cells in culture or in micronuclei in mouse bone marrow.

The Committee also considered some additional data on the fate of konjac flour in the large intestine, including the results of a recent study using human faecal flora *in vitro*, which showed that extensive hydrolysis of konjac flour occurs in the large intestine. Konjac flour underwent less fermentation than D-glucose, D-galactose, soluble starch, pectin and guar gum, but more than xanthan gum, L-glucose, carboxymethylcellulose and sodium alginate. Although only indirect evidence was provided, the Committee concluded that konjac flour, like other polysaccharide gums, undergoes fermentation in the large intestine to fatty acids (primarily acetate, propionate and butyrate).

The Committee reviewed data from animal and human studies on the effect of konjac flour and other polysaccharide gums on the absorption of fat-soluble vitamins and cholesterol and the reabsorption of bile acids. The available data indicate that konjac flour affects the absorption of vitamin E and cholesterol only at high doses (possibly through interference with bile acid micelle formation and subsequent interference with transport mechanisms). The Committee noted that definitive studies to establish the threshold dose of konjac flour that affects vitamin E absorption had still not been carried out, but considered that it was likely to be much higher than the levels of intake of konjac flour when used as a food additive.

The Committee stressed that this evaluation applies only to the use of konjac flour as a food additive, and concluded that the additional studies provided no evidence of adverse effects in experimental animals. The metabolic fate of konjac flour in the intestine is similar to that of other polysaccharide gums. On the basis of this reassessment and the anticipated food additive uses of konjac flour (as a thickener, emulsifier, stabilizer, gelling agent, texturizer and glazing agent), the Committee established an ADI "not specified" for konjac flour.

A monograph addendum was prepared. The existing specifications were revised, with minor changes.

3.6 Miscellaneous substances

3.6.1 *Benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and the benzoate salts*

All of these substances have been evaluated previously by the Committee, as the individual substances. Because of their structural similarity and common metabolic fate, however, a group ADI has been established for these substances. With the exception of benzoic acid and the benzoate salts, which are used as food preservatives, all of these substances are used as flavouring agents. Benzyl alcohol is also used as a carrier solvent.

At its forty-first meeting (Annex 1, reference *107*), the Committee recommended that a full review of benzyl acetate, benzoic acid, the benzoate salts, benzaldehyde and benzyl alcohol be performed in 1995 to determine whether reproductive toxicity/teratogenicity studies or other studies would be required.

At its present meeting, the Committee reviewed data from studies on disposition and metabolism, short-term and long-term toxicity, genotoxicity, reproductive toxicity, teratogenicity and observations in humans. On the basis of this review, a number of issues were identified which are important in the safety evaluation of these compounds. Since they are all metabolized to benzoic acid, it was considered reasonable to assume that the results of studies on one member of the group would apply to all the others.

The results of a number of studies in humans and experimental animals indicated that the formation of hippuric acid from benzoic acid is a saturable process in which the availability of glycine is the rate-limiting step. This observation is particularly relevant to the interpretation of the toxic effects of these compounds in experimental animals, since supplementation of the diet with glycine was shown to alleviate the toxic effects of high doses of benzyl acetate and benzoic acid, including reductions in body-weight gain and neurotoxicity. However, even with saturation of hippuric acid formation, clearance of compounds in the benzyl group is relatively rapid in both experimental animals and humans. An extensive review of the toxicity of benzoate showed that at high doses it interferes with intermediary metabolism, including the urea cycle, gluconeogenesis, fatty acid metabolism, and the tricarboxylic acid cycle, probably by sequestering coenzyme A prior to its conjugation with glycine. This is consistent with the observation of effects such as metabolic acidosis, convulsions, and hyperpnoea in experimental animals and humans given very high doses of this substance.

Administration of benzyl acetate to rats by gavage was shown to result in higher peak plasma levels of benzoic acid in comparison with ingestion of a similar daily dose in the diet, while plasma levels of hippuric acid were similar regardless of the route of administration. The toxicity of benzyl acetate was also higher when it was administered by gavage than when it was given in the diet. Since depletion of glycine may be a major factor in the toxic effects observed at the high doses used in animal studies, the Committee considered that it would be inappropriate to extrapolate the results of gavage studies to humans. It also considered that depletion of glycine might be of concern with respect to the developing fetus and neonate. It was noted that benzoic acid and hippuric acid are generated as a result of phenylalanine and tyrosine metabolism.

Long-term studies in which benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and sodium benzoate were administered in the feed or by gavage to mice and rats were available for review by the Committee. No definitive conclusions could be drawn from carcinogenicity studies of sodium benzoate in mice and rats, as the information provided was insufficient for this purpose, and survival rates in the study in rats were too low to allow it to be considered as conclusive. The Committee reviewed the studies evaluated in the previous monographs and an additional study in which benzaldehyde was administered in corn oil by gavage to rats at 200 or 400 mg per kg of body weight per day for 103 weeks and to mice at 200 or 400 mg per kg of body weight per day (males), or 300 or 600 mg per kg of body weight per day (females) for 103 weeks. On the basis of these studies, the Committee concluded that neither benzyl acetate nor benzyl alcohol is carcinogenic. As in the studies in mice and rats given benzyl acetate in corn oil by gavage, increased incidences of pancreatic acinar cell adenomas in rats and of papillomas of the forestomach in mice were noted after administration of benzaldehyde. However, as in its previous review of benzyl acetate, the Committee concluded that the results of studies in which the compound was administered in the diet were more relevant to its safety assessment as a food additive than those in which it was given in corn oil by gavage.

The Committee also reviewed data from genotoxicity studies. None of the four compounds was mutagenic in the Ames test, either with or without metabolic activation. The compounds all induced gene mutations in the mouse lymphoma assay at the thymidine kinase locus (benzoic acid was not tested), although the requirement for metabolic activation varied. Some weak clastogenic activity was noted in *in vitro* assays, but not in *in vivo* assays.

Several studies addressing aspects of the potential teratogenicity and reproductive toxicity of benzyl acetate, benzyl alcohol, benzaldehyde and sodium benzoate were reviewed. Delayed development and reduced fetal and postnatal pup body weights were observed in developmental toxicity studies in rats, mice, hamsters and rabbits, but only at doses that were toxic to the mother. In a teratogenicity study with sodium benzoate, doses that induced severe maternal toxicity were associated with embryotoxic and fetotoxic effects and fetal malformations. A 4-generation study in rats showed no effect on growth, fertility, lactation or survival.

The Committee was aware of reports of idiosyncratic human intolerance to benzoate, but these were not considered relevant to the establishment of an ADI for this group of compounds. The Committee endorsed the view expressed in the report of its twenty-seventh meeting (Annex 1, reference *62*) that appropriate labelling is a feasible means of offering protection to susceptible individuals.

The Committee was satisfied that the data reviewed for compounds in this group were sufficient to demonstrate the lack of teratogenic, reproductive or carcinogenic potential. Consequently, the Committee concluded that further studies were not required, and the group ADI of 0–5 mg per kg of body weight as benzoic acid equivalents was maintained.

A toxicological monograph was prepared. The existing specifications for benzoic acid, the benzoate salts (calcium, potassium and sodium), benzaldehyde, benzyl acetate, benzyl alcohol and benzyl benzoate were revised, with minor changes.

Benzyl alcohol is used as both a flavouring agent and a carrier solvent. The specifications for this compound were therefore retained in the form of a monograph, in addition to being incorporated in the table on specifications for flavouring agents (see section 2.3.5).

3.6.2 *Sucrose acetate isobutyrate*

Sucrose acetate isobutyrate was evaluated previously by the Committee at its nineteenth, twenty-first, twenty-sixth and forty-first meetings (Annex 1, references *38*, *44*, *59* and *107*). At the forty-first meeting, a temporary ADI of 0–10 mg per kg of body weight was allocated, pending the submission of information that would clarify the disparate effects of sucrose acetate isobutyrate on hepatobiliary function in the dog compared with other species, in particular, humans.

In the dog, doses as low as 0.5% of the diet (equivalent to 125 mg per kg of body weight per day) were associated with the development of

increased serum alkaline phosphatase activity, impairment of biliary excretion as indicated by decreased bromosulfophthalein clearance, a marked increase in the activity of several enzymes in the bile canaliculi, increased liver weights, and microscopic changes in hepatocellular morphology after 12 weeks. All of the effects noted in these short-term studies were reversible within 3–6 weeks after withdrawal of sucrose acetate isobutyrate from the diet. The effect of oral administration of sucrose acetate isobutyrate on biliary excretion in the dog was further investigated in a series of liver function tests. A single oral dose of 25 mg per kg of body weight was shown to reduce clearance of bromosulfophthalein and a very slight effect was still apparent at 5 mg per kg of body weight, although this was considered to be the NOEL by the Committee at its forty-first meeting (Annex 1, reference *107*).

None of these hepatic effects was observed in the rat or monkey in studies lasting up to 1 year at dose levels of up to 2000 and 2400 mg per kg of body weight per day, respectively, nor did tests of liver function indicate impairment of biliary excretion. In humans, sucrose acetate isobutyrate given orally at a dose of 20 mg per kg of body weight per day for 14 days did not result in changes in the activities of serum enzymes that are markers for liver damage nor in the clearance of bromosulfophthalein.

The existing data on sucrose acetate isobutyrate were re-evaluated at the present meeting. Data on the disposition of sucrose acetate isobutyrate in rats, dogs and humans indicate differences between these species, humans resembling the rat rather than the dog. Dogs excrete more highly acylated sucrose molecules in the urine and bile than do rats and humans (data only for urinary excretion) and (at least for the form of sucrose acetate isobutyrate of highest relative molecular mass, sucrose octaisobutyrate), excrete a higher proportion of the dose in the bile than does the rat. In addition, in humans there was no effect on indices of hepatobiliary function at a dose of 20 mg per kg of body weight per day, a dose which exceeds the NOEL of 5 mg per kg of body weight for impairment of bromosulfophthalein clearance in the dog.

The Committee concluded that the effects of sucrose acetate isobutyrate on hepatobiliary excretion in the dog were not relevant for humans. Therefore, an ADI of 0–20 mg per kg of body weight was allocated, based on the NOEL in the long-term study in rats of 2000 mg per kg of body weight per day and a safety factor of 100.

A toxicological monograph was not prepared. The existing specifications were revised, with minor changes.

4. Contaminants: aflatoxins

Aflatoxins B_1, B_2, G_1 and G_2 are produced in plants and plant products contaminated by three *Aspergillus* species: *A. flavus*, *A. parasiticus* and the rare species, *A. nomius*. Aflatoxins M_1 and M_2, the hydroxylated metabolites of aflatoxins B_1 and B_2, occur predominantly in the milk of cows fed rations containing aflatoxins B_1 and B_2. However, aflatoxin B_1 is usually found in the greatest concentration in the food supply, and most of the available toxicological data relate to this compound.

The aflatoxins were previously evaluated at the thirty-first meeting of the Committee (Annex 1, reference *77*). At that time, the Committee considered aflatoxin to be a potential human carcinogen, and urged that the intake of dietary aflatoxin be reduced to the lowest practicable levels, so as to reduce the potential risk as far as possible. A working group convened by the International Agency for Research on Cancer also concluded that naturally occurring aflatoxins are carcinogenic to humans (*32*).

At its present meeting, the Committee reviewed a wide range of toxicity studies in animals that provided both qualitative and quantitative information on the above-mentioned aflatoxins. These studies showed that aflatoxins produce primary liver cancer in animals, the carcinogenic potency varying widely from species to species and among the various toxins.

Most of the epidemiological studies show a correlation between exposure to aflatoxin B_1 and primary liver cancer, although there are some conflicting results. However, other factors are also associated with an increased risk of primary liver cancer in humans, most notably carriage of hepatitis B virus. The risk associated with exposure to aflatoxins appears to be enhanced by simultaneous exposure to hepatitis B virus or possibly hepatitis C virus. This interaction affects the potency and possibly also the biochemistry of the aflatoxins. Many other etiological agents for primary liver cancer may also interact with exposure to aflatoxins, making it difficult to interpret the epidemiological studies in the context of aflatoxins alone.

The Committee was requested to estimate the carcinogenic potency of aflatoxins and to derive estimates of the potential risks for different human populations. Therefore, despite the difficulties in interpreting the results of the available epidemiological studies on aflatoxins, it seemed appropriate to use these data on humans for this purpose.

If the potential risks of exposure to aflatoxins are to be assessed, potency estimates derived from human studies must be combined

with estimates of aflatoxin intake derived from data on the consumption of affected commodities and levels of aflatoxins in those commodities. The level of aflatoxin contamination of foodstuffs, however, varies widely both temporally and geographically, and is affected by a variety of factors, as discussed at the thirty-first meeting (Annex 1, reference 77). The intake of aflatoxins also varies widely with diet. Further development of biochemical markers may help to clarify the level of intake. A major current source of uncertainty in the data on aflatoxin levels is local assessment of the level of aflatoxin contamination in food produced and used locally.

Thus, although potency and intake can be estimated for aflatoxins, and these estimates can be used for calculating the risks for various human populations, such calculations involve considerable uncertainty.

The Committee considered all of these factors in estimating the potential risks of exposure to the aflatoxins; however, the task could not be completed at the present meeting. In view of the value of such estimates, the Committee recommended that assessment of the carcinogenic potency of aflatoxins and the potential risks associated with their intake be continued at its next meeting and that a monograph be published summarizing the data and analyses. The Committee also recommended that the refined models for assessing intake of aflatoxins be included in the risk assessment as they become available. In the meantime, the Committee reiterated its previous recommendation that exposure to aflatoxins should be reduced to the lowest practicable levels, so as to reduce, as far as possible, the potential risk. In this regard, the Committee considered that the measures for minimizing aflatoxin contamination of food that were described in the report of its thirty-first meeting (Annex 1, reference 77) were still highly relevant.

5. Revision of certain specifications

A total of 34 substances were examined for specifications only (see Annex 2), and the specifications for 29 were revised. The existing specifications for the polyols were revised as a group, taking into account the availability of more comprehensive analytical methods. This review was undertaken in conjunction with the evaluation of the toxicological significance of the proliferative lesions of the adrenal medulla observed in rats given these substances (section 2.2.4). The specifications for isomalt were revised to include products obtained by an alternative purification step. For lactitol, the "tentative" designa-

tion for the specifications was deleted, as the required information was forthcoming.

The specifications for citric acid, lactic acid, propylene glycol, calcium stearoyl-2-lactylate, sodium stearoyl-2-lactylate and triacetin were revised, with minor corrections.

The specifications for acesulfame potassium were revised and criteria for organic impurities were included.

The Committee agreed that the existing specifications for annatto extracts were in need of revision with a view to covering oil- and alkali-extracted products separately from solvent-extracted products. Therefore, the existing specifications for annatto extracts were revised to cover oil- and alkali-extracted products only, and new specifications were prepared to cover solvent-extracted products.

The existing specifications for ammonium hydroxide were revised and the title changed to ammonia solution.

The existing tentative specifications for calcium dihydrogen phosphate were revised and the "tentative" designation was deleted.

The specifications for cyclohexylsulfamic acid (cyclamic acid) and its calcium and sodium salts were reviewed and the limits for cyclohexylamine and dicyclohexylamine were decreased. A request for the addition of a limit for aniline was rejected as no test for this substance was forthcoming.

The tentative specifications for enzyme-treated starches were on the agenda for revision. However, as no new information was received, the Committee decided to maintain the "tentative" qualification, and requested new information for evaluation in 1997. Unless this information is received, the specifications will be withdrawn.

The Committee agreed that hydrochloric acid produced during the manufacture of chlorinated hydrocarbon pesticides was not to be considered to be of food-grade quality. A purity criterion limiting the occurrence of total organic compounds was added to the specifications for this substance.

The existing specifications for microcrystalline cellulose were revised in order to limit the product to materials with a particle size of not less than 5 μm. Some other minor changes were also made.

The existing specifications for propylene glycol esters of fatty acids were revised and designated as "tentative". The Committee requested a method of assay for the total ester content for evaluation in 1997.

The existing specifications for sodium polyphosphates, glassy, were revised in order to define the soluble product specifically. New specifications were prepared for sodium metaphosphate, insoluble.

The existing specifications for stearyl tartrate were revised in order to describe the material more accurately. The "tentative" designation was deleted.

The Committee noted that the existing specifications for tartaric, acetic and fatty acid esters of glycerol, mixed (Annex 1, reference *12*), were out of date and incomplete. New specifications were therefore prepared and designated as "tentative". The Committee decided to request information on methods of manufacture for evaluation in 1997 in order to distinguish this material from diacetyltartaric and fatty acid esters of glycerol (DATEM). When this information is available the two related substances will be evaluated together to decide whether the ADIs of the two materials should be different or the same.

The Committee considered a request to prepare specifications for carboxymethyl cellulose, enzyme-hydrolysed. However, the Committee understood that this product was not yet on the market and decided to defer the establishment of specifications until such time as it is known to be commercially available.

6. Recommendations

1. In view of the large number of food additives and contaminants requiring evaluation or re-evaluation, the important role that the recommendations of the Committee play in the development of international food standards and of regulations in many countries, and the need for maintaining consistency and continuity within the Committee, it is strongly recommended that meetings of the Joint FAO/WHO Expert Committee on Food Additives continue to be held at least once yearly to evaluate these substances.
2. In view of the importance of identity and purity specifications in defining the products being considered in safety assessments, and their significance for the national food legislation of many FAO/WHO Member States, the Committee emphasized the need for the regular updating and compilation of the *Compendium of food additive specifications* (Annex 1, reference *96*) and the *Guide to specifications* (Annex 1, reference *100*).
3. In view of the usefulness of the safety evaluation procedure used at the present meeting for evaluating the three groups of flavouring

agents, the Committee recommended that the procedure be applied to groups of flavouring agents to be evaluated at future meetings. It also recommended that step 5(b) of the original procedure be considered as soon as possible.

4. The Committee recommended that FAO and WHO continue to develop searchable databases on substances that have been evaluated by the Committee (e.g. on CD-ROM). Such databases would be of considerable use to regulatory authorities, industry and other interested parties worldwide. It was noted that the International Programme on Chemical Safety is producing a CD-ROM that includes recent information on the evaluations performed by the Committee, and the FAO and WHO homepages on the World-Wide Web will soon include summaries of the evaluations made by the Committee. Use of these homepages will provide timely information to interested parties and offer a rapid means of obtaining information on food additives and contaminants evaluated by the Committee.

5. The Committee recommended that the Codex Alimentarius Commission distinguish between substances when including them in the International Numbering System (INS) list. This would avoid confusion between substances that are assigned the same number, such as sorbitol and sorbitol syrup.

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Annex 1

Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

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2. *Procedures for the testing of intentional food additives to establish their safety for use* (Second report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. *Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants)* (Third report of the Expert Committee). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, vol. I. *Antimicrobial preservatives and antioxidants*. Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
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30. *Evaluation of certain food additives and the contaminants mercury, lead and cadmium* (Sixteenth report of the Expert Committee). FAO Nutrition Meetings Report Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.
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95. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 28, 1991.
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Annex 2

Acceptable Daily Intakes, other toxicological information, and information on specifications

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg per kg of body weight and other toxicological recommendations
Antioxidants		
Dodecyl gallate	R	No ADI allocated[b]
Octyl gallate	R	
Propyl gallate	R	0–1.4
Emulsifier		
Glycerol ester of wood rosin	R	0–25
Flavouring agents		
Ethyl esters		
Ethyl formate	R	No safety concern at current levels of intake[c]
Ethyl acetate	R	No safety concern at current levels of intake[d]
Ethyl propionate	N	
Ethyl butyrate	R	
Ethyl pentanoate	N	No safety concern at current levels of intake[c]
Ethyl hexanoate	N	No safety concern at current levels of intake[d]
Ethyl heptanoate	R	No safety concern at current levels of intake[c]
Ethyl octanoate	N	
Ethyl nonanoate	R	
Ethyl decanoate	N	
Ethyl undecanoate	N, T	
Ethyl dodecanoate	R	
Ethyl tetradecanoate	N	
Ethyl hexadecanoate	N	
Ethyl octadecanoate	N	
Isoamyl alcohol and related esters		
Isoamyl alcohol	N	No safety concern at current levels of intake[c]
Isoamyl formate	N	
Isoamyl acetate	R	No safety concern at current levels of intake[d]
Isoamyl propionate	N	No safety concern at current levels of intake[c]
Isoamyl butyrate	R	No safety concern at current levels of intake[d]
Isoamyl hexanoate	N	No safety concern at current levels of intake[c]
Isoamyl octanoate	N, T	
Isoamyl nonanoate	N, T	

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg per kg of body weight and other toxicological recommendations
Isoamyl isobutyrate	N	No safety concern at current levels of intake[c]
Isoamyl isovalerate	N	
Isoamyl 2-methylbutyrate	N, T	
Allyl esters		
Allyl propionate	N, T	No safety concern at current levels of intake[e]
Allyl butyrate	N	
Allyl hexanoate	R	No safety concern at current levels of intake[f]
Allyl heptanoate	R	No safety concern at current levels of intake[e]
Allyl octanoate	N	
Allyl nonanoate	N	
Allyl isovalerate	R	
Allyl sorbate	N, T	
Allyl 10-undecanoate	N	
Allyl tiglate	R	
Allyl 2-ethylbutyrate	N	
Allyl cyclohexaneacetate	N, T	
Allyl cyclohexane-propionate	R	
Allyl cyclohexanebutyrate	N, T	
Allyl cyclohexanevalerate	N, T	
Allyl cyclohexane-hexanoate	N, T	
Allyl phenylacetate	N, T	
Allyl phenoxyacetate	N	No safety concern at current levels of intake[g]
Allyl cinnamate	N, T	No safety concern at current levels of intake[e]
Allyl anthranilate	N, T	No safety concern at current levels of intake[g]
Allyl 2-furoate	N, T	Evaluation not completed[h]
Sweetening agent		
Alitame	R	0–1[i]
Thickening agent		
Konjac flour	R	ADI "not specified" for food additive uses[j]
Miscellaneous substances		
Benzyl acetate	R	0–5 (group ADI)
Benzyl alcohol	R	
Benzaldehyde	R	
Benzoic acid and its salts	R	
Sucrose acetate isobutyrate	R	0–20

Contaminant	Toxicological recommendations
Aflatoxins	Evaluation not completed[k]

Substance (considered for specifications only)	Specifications[a]
Polyols	
Mannitol	R
Sorbitol	R
Xylitol	R
Isomalt	R
Lactitol	R
Maltitol	R
Maltitol syrup	R
Sorbitol syrup	R
Cyclohexylsulfamic acid and its salts	
Cyclohexylsulfamic acid	R
Calcium cyclamate	R
Sodium cyclamate	R
Miscellaneous substances	
Acesulfame potassium	R
Ammonia solution	R
Annatto extracts (oil- and alkali-extracted)	R
Annatto extracts (solvent-extracted)	N
Benzyl benzoate	R
Calcium dihydrogen phosphate	R
Calcium stearoyl-2-lactylate	R
Citric acid	R
Enzyme-hydrolysed carboxymethyl cellulose	O[l]
Enzyme-treated starches	S, T[m]
Ethanol	R
Gellan gum	R
Hydrochloric acid	R
Lactic acid	R
Microcrystalline cellulose	R
Propylene glycol	R
Propylene glycol esters of fatty acids	R, T[n]
Sodium metaphosphate, insoluble	N
Sodium polyphosphates, glassy	R
Sodium stearoyl-2-lactylate	R
Stearyl tartrate	R
Tartaric, acetic and fatty acid esters of glycerol, mixed	N, T[o]
Triacetin	R

Notes to Annex 2

(a) N, new specifications prepared; O, no specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; and T, the existing, new or revised specifications are tentative and comments are invited.

(b) *Dodecyl and octyl gallate.* The temporary ADI was not extended because the additional studies on the pharmacokinetics and metabolism of dodecyl and octyl gallate requested at the forty-first meeting of the Committee (WHO Technical Report Series, No. 837) were not available.

(c) This flavouring agent is in structural class I; the conclusions are based on a "yes" answer at step 2 and a "no" answer at step 3(a) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report).

(d) This flavouring agent is in structural class I; the conclusions are based on "yes" answers at steps 2, 3(a) and 4(a) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report).

(e) This flavouring agent is in structural class II; the conclusions are based on "no" answers at steps 2 and 3(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report). When step 4(b) of the modified approach was applied (see Fig. 2), the Committee concluded that an adequate margin of safety existed between the NOEL and current levels of intake.

(f) This flavouring agent is in structural class II; the conclusions are based on a "no" answer at step 2 and a "yes" answer at step 3(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report). It was evaluated on the basis of the available toxicity data.

(g) This flavouring agent is in structural class III; the conclusions are based on "no" answers at steps 2 and 3(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996 and modified at the present meeting (see section 2.2.1 of the main report). When step 4(b) of the modified approach was applied (see Fig. 2), the Committee concluded that an adequate

margin of safety existed between the NOEL and current levels of intake.

(h) *Allyl 2-furoate.* The evaluation was postponed, pending consideration of step 5(b) of the approach described in Annex 5 of WHO Food Additives Series, No. 35, 1996, at a future meeting of the Committee at which food additives and contaminants are evaluated. The Committee requested additional toxicity data on this substance.

(i) *Alitame.* The results of an ongoing study of tolerance to repeated doses of alitame in diabetic subjects should be submitted for assessment when available.

(j) *Konjac flour.* Includes uses as a thickener, emulsifier, stabilizer, and gelling, texturizing and glazing agent.

(k) *Aflatoxins.* The evaluation could not be completed at the present meeting. The Committee recommended that assessment of the carcinogenic potential of aflatoxins and the potential risks associated with intake be continued at the next meeting of the Committee at which food additives and contaminants are evaluated.

(l) *Enzyme-hydrolysed carboxymethyl cellulose.* The Committee considered a request to prepare specifications for this substance. However, the Committee understood that this product was not yet on the market, and decided to defer the establishment of specifications until such time as it is known to be commercially available.

(m) *Enzyme-treated starches.* The tentative specifications for enzyme-treated starches were on the agenda for revision. However, as no new information was received, the Committee decided to maintain the "tentative" qualification, and requested new information for evaluation in 1997. Unless this information is received, the specifications will be withdrawn.

(n) *Propylene glycol esters of fatty acids.* The existing specifications for propylene glycol esters of fatty acids were revised and designated as "tentative". The Committee requested a method of assay for the total ester content for evaluation in 1997.

(o) *Tartaric, acetic and fatty acid esters of glycerol, mixed.* The Committee noted that the specifications for tartaric, acetic and fatty acid esters of glycerol, mixed, in FAO Nutrition Meetings Report Series, No. 40A, B, C, 1967, were out of date and incomplete. New specifications were therefore prepared and

designated as "tentative". The Committee requested information on methods of manufacture for evaluation in 1997 in order to distinguish this material from diacetyltartaric and fatty acid esters of glycerol (DATEM).

Annex 3
Toxicological data on ethyl and isoamyl esters

The ethyl and isoamyl esters evaluated at the present meeting of the Committee were considered to be of no safety concern on the basis of structural class, the low estimated intakes and, where appropriate, their metabolism to endogenous substances. Consequently, no toxicity data were necessary for application of the modified procedure for flavouring agents discussed in section 2.2.1 of the main report. Nevertheless, the Committee believed that it was useful to include the toxicity data on these substances as an annex to the report.

Ethyl esters

The component alcohol, ethanol, was evaluated by the Committee at its fourteenth meeting, when an ADI limited by Good Manufacturing Practice was established for ethanol for use as an extraction solvent (Annex 1, reference *26*). It is absorbed rapidly and completely oxidized via well-known metabolic pathways. There is endogenous synthesis of ethanol, since it is present in the serum of subjects who have abstained from alcohol ingestion. Low concentrations of ethanol are metabolized rapidly, and the endogenous concentrations detected in serum correspond to the formation of about 2.5–5 g per day (*1*, *2*). The estimated per capita intake of ethanol derived from the ethyl esters is about 25–30 mg per day (*3*, F. Grundschober, personal communication, 1996).

Short-term studies on ethyl formate, ethyl hexanoate, ethyl heptanoate, ethyl octanoate and ethyl nonanoate in rats showed no adverse effects at daily doses of up to 500 mg per kg of body weight in the diet for 13–17 weeks (*4*). Ethyl acetate given in drinking-water to rats for 56 weeks did not produce adverse effects at a dose corresponding to 4 mg per kg of body weight per day (*5*). The Committee was aware of studies in which high doses of a number of carboxylic acids had been given to rats and had resulted in forestomach lesions (*6–8*). However, the studies were considered not to be relevant to the ingestion of esters as flavouring agents.

Ethyl formate

Ethyl formate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference *50*). At that meeting, the Committee concluded that ethyl formate could be included in the group ADI with

formic acid of 0–3 mg per kg of body weight (expressed as formic acid) on the basis of the available short-term studies, metabolic studies, and toxicological data on formic acid and formic acid esters.

Formic acid was reported not to produce adverse effects in long-term experiments in rats at daily doses of up to the equivalent of 500 mg per kg of body weight for up to 3 years (*9*).

Ethyl acetate

Ethyl acetate was evaluated by the Committee at its eleventh meeting (Annex 1, reference *14*). At that time, an ADI of 0–25 mg per kg of body weight was established for this compound on the basis of its known metabolic fate. No toxicological data were available for evaluation. In a more recent study, no adverse effects were reported when rats were given a drinking-water–fusel oil mixture containing ethyl acetate at a dose corresponding to 4 mg per kg of body weight per day for 56 weeks (*5*).

Acetic acid was last evaluated by the Committee at its seventeenth meeting (Annex 1, reference *32*), when an ADI "not limited" was established for this compound on the basis of its known metabolic pathway and its consumption as a normal constituent of the human diet.

Ethyl propionate

Ethyl propionate has not been previously evaluated by the Committee. Propionic acid was last evaluated by the Committee at its seventeenth meeting (Annex 1, reference *32*), when an ADI "not limited" was established for this compound on the basis of available biochemical and toxicological studies and knowledge of its role in normal metabolism.

Ethyl butyrate

Ethyl butyrate was evaluated by the Committee at its eleventh meeting (Annex 1, reference *14*). At that meeting, an ADI of 0–15 mg per kg of body weight was established for this substance on the basis of a short-term study in rats and information on its hydrolysis into normal constituents of food. Butyric acid has not been previously evaluated by the Committee.

Ethyl pentanoate (valerate)

Neither ethyl pentanoate nor pentanoic acid has been previously evaluated by the Committee.

Ethyl hexanoate (caproate)

Neither ethyl hexanoate nor hexanoic acid has been previously evaluated by the Committee.

Ethyl heptanoate (enanthate)

Ethyl heptanoate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference *50*). At that time, an ADI of 0–2.5 mg per kg of body weight was established for this substance on the basis of a short-term study in rats and data on its metabolic fate.

Ethyl octanoate (caprylate)

Ethyl octanoate has not been previously evaluated by the Committee. No adverse effects were observed when rats were fed ethyl octanoate at dose levels of up to 1% in the diet (equivalent to 500 mg per kg of body weight per day) for 17 weeks (*4*).

Salts of octanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference *70*), when an ADI "not specified" was established on the basis of the occurrence of their corresponding acids in edible fats and oils, their long history of use as foods or food components, and knowledge of their metabolic pathway.

Ethyl nonanoate (pelargonate)

Ethyl nonanoate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference *50*), when an ADI of 0–2.5 mg per kg of body weight was established for this substance on the basis of a short-term study in rats and data on its metabolic fate.

Ethyl decanoate (caprate)

Ethyl decanoate has not been previously evaluated by the Committee.

Salts of decanoic acid were evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference *70*). At that meeting, an ADI "not specified" was established for these compounds on the basis of the occurrence of their corresponding acids in edible fats and oils, their long history of use as foods or food components, and knowledge of their metabolic pathway.

Ethyl undecanoate

Ethyl undecanoate has not been previously evaluated by the Committee.

Ethyl dodecanoate (laurate)

Ethyl dodecanoate was last evaluated by the Committee at its twenty-third meeting (Annex 1, reference *50*). At that meeting, the Committee established an ADI of 0–1 mg per kg of body weight for this substance on the basis of information on its hydrolysis into dodecanoic acid and ethanol, the known toxicity of ethanol and the ready metabolism of dodecanoic acid, a naturally occurring fatty acid.

Salts of dodecanoic acid were evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference *70*), when an ADI "not specified" was established on the basis of the occurrence of their corresponding acids in edible fats and oils, their long history of use as foods or food components, and knowledge of their metabolic pathway. No adverse effects were reported when dodecanoic acid was given to rats at a dose level of approximately 5000 mg per kg of body weight per day for 18 months (*10*).

Ethyl tetradecanoate (myristate)

Ethyl tetradecanoate has not been previously evaluated by the Committee.

Salts of tetradecanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference *70*), when an ADI "not specified" was established. Tetradecanoic acid is common in the triglyceride part of fats and oils used for human consumption.

Ethyl hexadecanoate (palmitate)

Ethyl hexadecanoate has not been previously evaluated by the Committee.

Salts of hexadecanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference *70*), when an ADI "not specified" was established. Hexadecanoic acid is one of the major saturated fatty acids in the triglyceride part of fats and oils used for human consumption.

Ethyl octadecanoate (stearate)

Ethyl octadecanoate has not been previously evaluated by the Committee.

Salts of octadecanoic acid were last evaluated by the Committee at its twenty-ninth meeting (Annex 1, reference *70*), when an ADI "not specified" was established. Octadecanoic acid is one of the major saturated fatty acids in the triglyceride part of fats and oils used for human consumption.

Isoamyl esters

Short-term studies on the parent alcohol, isoamyl alcohol, in rats showed no adverse effects at daily doses of 1000 mg per kg of body weight by gavage for 17 weeks (*11*) or 2000 mg per kg of body weight in drinking-water for 53–56 weeks (*5*). The only ester for which a similar adequate study was available was isoamyl isovalerate. No adverse effects were observed in rats given isoamyl isovalerate in the diet at 22, 70 or 220 mg per kg of body weight per day for 13 weeks, as indicated by the results of biochemical analyses of blood and urine, organ weights, and histopathological examination (*12*).

Toxicity data from studies on the carboxylic acid components of isoamyl esters gave no evidence of systemic toxicity at daily doses of at least 400 mg per kg of body weight (*8*, *9*, *13*).

Further information on formic, acetic, propionic and butyric acids is given under ethyl esters (see above).

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SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.9
Revision Date 20.01.2025
Print Date 03.12.2025
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name	:	Cognac oil
Product Number	:	W233218
Brand	:	Aldrich
REACH No.	:	A registration number is not available for this substance as the substance or its uses are exempted from registration or the annual tonnage does not require a registration.
CAS-No.	:	8016-21-5

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Merck Life Science Sp. z o.o Pastelowa 8 PL-60-198 POZNAN
Telephone	:	+48 61 8290-100
Fax	:	+48 61 8290-120
E-mail address	:	TechnicalService@merckgroup.com

1.4 Emergency telephone

Emergency Phone #	:	+(48)-223988029 (CHEMTREC) 112 (numer alarmowy)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Skin irritation, (Category 2)	H315: Causes skin irritation.
Eye irritation, (Category 2)	H319: Causes serious eye irritation.

2.2 Label elements

Labelling according Regulation (EC) No 1272/2008

Pictogram

Signal Word Warning

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Hazard Statements	
H315	Causes skin irritation.
H319	Causes serious eye irritation.
Precautionary Statements	
P264	Wash skin thoroughly after handling.
P280	Wear protective gloves/ eye protection/ face protection.
P302 + P352	IF ON SKIN: Wash with plenty of water.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P332 + P313	If skin irritation occurs: Get medical advice/ attention.
P337 + P313	If eye irritation persists: Get medical advice/ attention.
Supplemental Hazard Statements	none

Reduced Labeling (<= 125 ml)

Pictogram

Signal Word	Warning
Hazard Statements	none
Precautionary Statements	none
Supplemental Hazard Statements	none

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

Ecological information:
The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.
Toxicological information:
The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

SECTION 3: Composition/information on ingredients

3.1 Substances

Synonyms : Vitis Vinifera

CAS-No. : 8016-21-5
EC-No. : 232-403-4

Component	Classification	Concentration
Cognac oil		
CAS-No. 8016-21-5 EC-No. 232-403-4	Skin Irrit. 2; Eye Irrit. 2; H315, H319	<= 100 %

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For the full text of the H-Statements mentioned in this Section, see Section 16.

SECTION 4: First aid measures

4.1 Description of first-aid measures

General advice
Show this material safety data sheet to the doctor in attendance.

If inhaled
After inhalation: fresh air.

In case of skin contact
In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact
After eye contact: rinse out with plenty of water. Call in ophthalmologist. Remove contact lenses.

If swallowed
After swallowing: immediately make victim drink water (two glasses at most). Consult a physician.

4.2 Most important symptoms and effects, both acute and delayed

The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed

No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Foam Carbon dioxide (CO2) Dry powder

Unsuitable extinguishing media
For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture

Nature of decomposition products not known.
Combustible.
Vapors are heavier than air and may spread along floors.
Forms explosive mixtures with air on intense heating.
Development of hazardous combustion gases or vapours possible in the event of fire.

5.3 Advice for firefighters

Stay in danger area only with self-contained breathing apparatus. Prevent skin contact by keeping a safe distance or by wearing suitable protective clothing.

5.4 Further information

Remove container from danger zone and cool with water. Prevent fire extinguishing water from contaminating surface water or the ground water system.

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SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Advice for non-emergency personnel: Do not breathe vapors, aerosols. Avoid substance contact. Ensure adequate ventilation. Keep away from heat and sources of ignition.
Evacuate the danger area, observe emergency procedures, consult an expert.
For personal protection see section 8.

6.2 Environmental precautions

Do not let product enter drains.

6.3 Methods and materials for containment and cleaning up

Cover drains. Collect, bind, and pump off spills. Observe possible material restrictions (see sections 7 and 10). Take up with liquid-absorbent material (e.g. Chemizorb®). Dispose of properly. Clean up affected area.

6.4 Reference to other sections

For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

Advice on protection against fire and explosion
Keep away from open flames, hot surfaces and sources of ignition.Take precautionary measures against static discharge.

Hygiene measures
Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Tightly closed.

Storage class
Storage class (TRGS 510): 10: Combustible liquids

7.3 Specific end use(s)

Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU). Safety glasses

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Skin protection
required

Body Protection
protective clothing

Respiratory protection
required when vapours/aerosols are generated.
Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.
Recommended Filter type: Filter type ABEK

The entrepeneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure
Do not let product enter drains.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Physical state	clear, liquid
b)	Color	colorless, green
c)	Odor	No data available
d)	Melting point/freezing point	No data available
e)	Initial boiling point and boiling range	No data available
f)	Flammability (solid, gas)	No data available
g)	Upper/lower flammability or explosive limits	No data available
h)	Flash point	66,7 °C - closed cup
i)	Autoignition temperature	No data available
j)	Decomposition temperature	No data available
k)	pH	No data available
l)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
m)	Water solubility	No data available
n)	Partition coefficient: n-octanol/water	No data available
o)	Vapor pressure	No data available
p)	Density	0,87 g/cm3 at 25 °C

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	Relative density	No data available
q)	Relative vapor density	No data available
r)	Particle characteristics	No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information
No data available

SECTION 10: Stability and reactivity

10.1 Reactivity
Forms explosive mixtures with air on intense heating.
A range from approx. 15 Kelvin below the flash point is to be rated as critical.

10.2 Chemical stability
The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
Strong heating.

10.5 Incompatible materials
Strong oxidizing agentsStrong oxidizing agents, Strong bases

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Mouse - > 5.000 mg/kg
Inhalation: No data available
Dermal: No data available

Skin corrosion/irritation
Remarks: No data available

Serious eye damage/eye irritation
Remarks: No data available

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
No data available

Carcinogenicity
No data available

Reproductive toxicity

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No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Endocrine disrupting properties

Product:

Assessment	The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

RTECS: RJ3690975
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

SECTION 12: Ecological information

12.1 Toxicity
No data available

12.2 Persistence and degradability
No data available

12.3 Bioaccumulative potential
No data available

12.4 Mobility in soil
No data available

12.5 Results of PBT and vPvB assessment
This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Endocrine disrupting properties

Product:

Assessment	:	The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

12.7 Other adverse effects
No data available

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SECTION 13: Disposal considerations

13.1 Waste treatment methods
No data available

SECTION 14: Transport information

14.1 UN number
ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name
ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)
ADR/RID: - IMDG: - IATA: -

14.4 Packaging group
ADR/RID: - IMDG: - IATA: -

14.5 Environmental hazards
ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user
No data available

Further information : No data available

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture
This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

Other regulations
Take note of Dir 94/33/EC on the protection of young people at work.

15.2 Chemical Safety Assessment
For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Full text of H-Statements

H315	Causes skin irritation.
H319	Causes serious eye irritation.

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Full text of other abbreviations

ADN - European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways; ADR - Agreement concerning the International Carriage of Dangerous Goods by Road; AIIC - Australian Inventory of Industrial Chemicals; ASTM - American Society for the Testing of Materials; bw - Body weight; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50 % of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; n.o.s. - Not Otherwise Specified; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; RID - Regulations concerning the International Carriage of Dangerous Goods by Rail; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TECI - Thailand Existing Chemicals Inventory; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative

Further information

The information is believed to be correct but is not exhaustive and will be used solely as a guideline, which is based on current knowledge of the chemical substance or mixture and is applicable to appropriate safety precautions for the product. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

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