ETHYL CARBAMATE

There appears to be no general consensus on a common trivial name for this substance: ethyl carbamate and urethane (or urethan) are both commonly used; however, a preference for ethyl carbamate was noted in the more recent literature. The name urethane is also sometimes applied to high-molecular-weight polyurethanes used as foams, elastomers and coatings. Such products are not made from and do not generate the chemical ethyl carbamate on decomposition. Due to this possible confusion, the term ethyl carbamate has been used in this monograph.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms*

CAS Registry No.*: 51–79–6*

Synonyms: Carbamic acid ethyl ester; ethylurethan; ethyl urethan; ethyl urethane; urethan; urethane

1.1.2 *Chemical formula and relative molecular mass*

$NH_2COOC_2H_5$ Relative molecular mass: 89.1

1.1.3 *Chemical and physical properties of the pure substance*

From Budavari (2000)

(a) Description: Colourless, almost odourless, columnar crystals or white granular powder; the pH of an aqueous solution is neutral

(b) Boiling-point: *182–184 °C*

(c) Melting-point: *48–50 °C*

(d) Solubility: Dissolves in water (1 g/0.5 mL), ethanol (1 g/0.8 mL), chloroform (1 g/0.9 mL), ether (1 g/1.5 mL), glycerol (1 g/2.5 mL) and olive oil (1 g/32 mL)

(e) Volatility: Sublimes readily at 103°C at 54 mm Hg; volatile at room temperature

1.1.4 *Technical products and impurities*

Trade names for ethyl carbamate include Leucothane, Leucethane and Pracarbamine.

The Chemical Catalogs Online database, produced by Chemical Abstracts Services, lists 37 suppliers for ethyl carbamate, which are predominantly situated in Europe, Japan and the USA. Technical grades with 98% purity as well as products with more than 99% purity (less than 0.1% ignitable residues) are available.

1.1.5 *Analysis*

The titration method described by Archer *et al*. (1948) was used to monitor patients who underwent therapy with ethyl carbamate. A gas chromatography–mass spectrometry (GC–MS) method to monitor ethyl carbamate in blood was developed by Hurst *et al*. (1990) to monitor the time course of elimination of ethyl carbamate in mice.

The methods developed to determine ethyl carbamate in various food matrices are summarized in Table 1.1; the analytical methodology was reviewed by Zimmerli and Schlatter (1991). GC coupled with MS seems to be the method of choice for this purpose. The overwhelming majority of methods involve quadrupole MS operating in selected-ion monitoring mode and the use of isotopically labelled internal standards. Validation data of collaborative studies are available (Dennis *et al*., 1990; Canas *et al*., 1994; Dyer, 1994; Hesford & Schneider, 2001; de Melo Abreu *et al*., 2005). In general, the validation results were judged to be satisfactory for the purpose of analysing ethyl carbamate in the lower microgram per kilogram range. The methods presented by Dyer (1994) and Canas *et al*. (1994) were adopted by the Association of Official Analytical Chemists International as part of their Official Methods. A collaborative analysis also led to the adoption of a method for the determination of ethyl carbamate in the European Community methods for the analysis of wine (European Commission, 1999).

The analysis of minor organic compounds in complex matrices, such as in spirit beverages, is difficult because of interferences by matrix components, even when extensive clean-up procedures are applied to the sample, e.g. extraction over diatomaceous earth columns, which is proposed by many authors. A possible approach to eliminate these interferences is the use of solid-phase extraction in combination with an improved chromatographic separation using multidimensional GC, as proposed by Jagerdeo *et al*. (2002) for the analysis of wine. However, this technique requires the time-consuming removal of ethanol before solid-phase extraction and specialized equipment consisting of GC with a flame-ionization detector and GC–MS, which are coupled using a cryo trap. As another approach, MS detection may be enhanced by application of tandem MS (MS–MS) to provide an improved sensitivity and specificity. Recently, it was demonstrated that low-cost bench-top triple quadruple mass spectrometers can be used in the routine analysis of ethyl carbamate in spirits (Lachenmeier *et al*., 2005a) or in bread (Hamlet *et al*., 2005).

Table 1.1 Methods for the analysis of ethyl carbamate in different matrices

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
Alcoholic beverages	–	Dilution to 10% vol, dichloromethane extraction	–	GC–ECD	DBWAX-30W	Low µg/kg range	Bailey *et al.* (1986)
	Methyl carbamate	Dichloromethane extraction	Extrelut	GC-NPD	Durabond-Wax	20	Baumann & Zimmerli (1986a)
	–	Dilution to 5% alcohol	Chemtube or Extrelut	GC (1) TEA (2) ECD (3) MS	CP Wax 52 CB	 (1) 1 (2) 2–5 (3) 1	Dennis *et al.* (1986, 1988)
	1,4-Butanediol or *N*,*N*-dimethylformamide	Salting-out with potassium carbonate	–	GC-MS EI or PCI	Carbowax 20M	EI: 100 PCI: 10	Bebiolka & Dunkel (1987)
	–	Dichloromethane extraction	–	GC–ECD, GC–MS	DBWAX	ECD: 5–10 MS: 0.5	Conacher *et al.* (1987)
	–	Dichloromethane extraction	–	GC–MS	DBWAX	0.5	Lau *et al.* (1987)
	n-Butyl carbamate	Dichloromethane extraction	Extrelut	GC–MS	WCOT, DBWAX	10	Mildau *et al.* (1987)
	–	Dilution to 10% vol, dichloromethane extraction	–	Two-dimensional GC–FID	(1) CP-SIL 5 CB (2) CP-WAX 52	1	van Ingen *et al.* (1987)
	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	Deactivated alumina	GC–TEA	DB-Wax	1.5	Canas *et al.* (1988)
	–	Dichloromethane extraction	–	GC–ion trap	Supelcowax 10	5	Clegg & Frank (1988)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
	Ethyl carbamate-d_5	Distillation, dichloromethane extraction	–	GC–MS	SGE BP 20	2-5	Funch & Lisbjerg (1988)
	tert-Butyl carbamate and *n*-butyl carbamate (GC–FID), [^{13}C,^{15}N]-ethyl carbamate	Dilution to 25% vol, dichloromethane extraction	Alumina clean-up	GC–FID GC–MS	DB-WAX Carbopack B/ Carbowax 20M	10-25 5	Pierce *et al*. (1988)
	Isopropyl carbamate	Dichloromethane extraction	–	Two-dimensional GC–TSD	BP-20, OV-1	1	Ma *et al*. (1995)
	–	Dilution to 20% vol	Derivatization with 9-xanthydrol	HPLC–fluorescence detection	HP AminoQuant	4.2	Herbert *et al*. (2002)
	Ethyl carbamate-d_5	Removal of ethanol	SPE (styrene–divinylbenzene copolymer)	GC–MS	HP-INNOWAX	3	Mirzoian & Mabud (2006)
Distilled spirits	Propyl carbamate	Evaporation with nitrogen	–	GC–MS	DB-Wax	10	Farah Nagato *et al*. (2000)
Grappa	Ethyl carbamate	Dichloromethane–ethyl acetate extraction	Derivatization with xanthydrol	GC–MS	DB 5	1	Giachetti *et al*. (1991)
Must and wine	–	–	–	FTNIR-screening	–	–	Manley *et al*. (2001)
Rice wine	Propyl carbamate	Chloroform extraction	Florisil	GC–MS	DB-Wax	–	Woo *et al*. (2001)
Spirits and mashes	–	Distillation	Chem-Elut 1020	GC–FID	(1) DB-Wax (2) DB-225	5	Wasserfallen & Georges (1987)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
Spirits	Pyrazole	Salting-out	–	GC–NPD	BC-CW 20 M	10	Adam & Postel (1987)
	n-Octanol	Ethyl acetate extraction	–	GC–FID	CP Wax 57 CB	10-20	Andrey (1987)
	tert-Butyl carbamate	Extraction with *n*-hexane–ethyl acetate mixture	Extrelut	GC–FID, GC–N-TSD	Stabilwax	50	Drexler & Schmid (1989)
	Propyl carbamate	–	–	GC–MS	FSOT	5	MacNamara *et al*. (1989)
	–	Salting-out	Filtration over activated carbon	GC–NPD, GC–FID	HP 19091 F-115 or Carbowax 20M	LOQ:1-5	Adam & Postel (1990)
	Ethyl carbamate-d_5	Dichloromethane extraction	Extrelut	GC–MS/MS	CP-wax	10	Lachenmeier *et al*. (2005a)
	–	–	–	FTIR screening	–	–	Lachenmeier (2005)
	Ethyl carbamate-d_5	Dilution 1:10	HS-SPME	GC–MS/MS	Stabilwax	30	Lachenmeier *et al*. (2006)
Whisky, sherry, port, wine	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	–	GC–MS/MS CI.	Carbowax SP-10	1	Brumley *et al*. (1988)
Wines and spirits	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	Florisil	GC–ECD, GC–MS/MS	Carbowax 20M Stabilwax		Cairns *et al*. (1987)
Wine	–	Chloroform extraction	Florisil	GC–ECD	GCQ, OV-17, Carbowax 1540	<100	Walker *et al*. (1974)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
	Propyl carbamate	Extraction with Soxhlet apparatus	–	GC–MS	DB-Wax	–	Fauhl & Wittkowski (1992)
	–	Dichloromethane extraction	Chem-Elut or Extrelut	GC–N-TEA	DB-Wax	1-2	Sen *et al*. (1992)
	Propyl carbamate	Dilution, dichloromethane extraction	Diatomaceous earth columns	GC–MS	Carbowax 20M	–	European Commission (1999)
	[^{13}C,^{15}N]-Ethyl carbamate	Removal of ethanol, dilution	SPE (styrene-divinylbenzene copolymer)	Two-dimensional GC–MS	HP-5MS DB-WAX	0.1	Jagerdeo *et al*. (2002)
	Propyl carbamate	–	MS–SPME	GC–MS	DB-Wax	9.6	Whiton & Zoecklein (2002)
Alcoholic beverages and foods	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	–	GC–MI/FTIR	DBWAX-30W	10	Mossoba *et al*. (1988)
Alcoholic beverages, fermented foods	*n*-Butyl carbamate	Pre-extraction with petroleum ether, dichloromethane extraction	Deactivated alumina	GC–FID	DB-Wax	6,7	Wang *et al*. (1997); Wang & Gow (1998)
Bread	Ethyl carbamate-d_5	Dichloromethane extraction	Extrelut	GC–MS/MS	EC-WAX	0.6	Hamlet *et al*. (2005)
Fermented foods	–	Dichloromethane extraction	Acid–celite column	GC–MS	CBP-20	0.5	Hasegawa *et al*. (1990)
Fermented Korean foods and beverages	Propyl carbamate	Various procedures	Various procedures	GC–MS	DB-Wax	11	Kim *et al*. (2000)

Table 1.1 (continued)

Sample matrix	Internal standard	Extraction principle	Clean-up	Detection	Column	LOD (µg/L)	Reference
Soya sauce	Propyl carbamate	Dichloromethane extraction	Extrelut	GC–MS	DB-Wax	1	Fauhl *et al.* (1993)
	–	Dichloromethane extraction	Celite columns	GC–MS	Supelcowax	0.5	Matsudo *et al.* (1993)
Blood	–	Before and after alkaline hydrolysis	–	Titration with 0.1 N sodium thiosulfate	–	–	Archer *et al.* (1948)
	[^{13}C,^{15}N]-Ethyl carbamate	Dichloromethane extraction	Chem-Elut 1000M	GC–MS	DB-WAX, DB-1	20	Hurst *et al.* (1990)

CI., chemical ionization; ECD, electrolytic conductivity detector; EI, electron ionization; FID, flame ionization detection; FTIR, Fourier transform infrared spectroscopy; FTNIR, Fourier transform near-infrared spectroscopy; GC, gas chromatography; HPLC, high-performance liquid chromatography; LOD, limit of detection; MI, matrix isolation; MS, mass spectrometry; NPD, nitrogen/phosphorus detector; PCI, positive chemical ionization; SPME, solid-phase microextraction; TEA, thermal energy analyser; TSD, thermoionic-specific detection

Solid-phase microextraction has recently emerged as a versatile solvent-free alternative to conventional extraction procedures. Ethyl carbamate has been analysed by HS–solid-phase microextraction only in wine samples (Whiton & Zoecklein, 2002) and spirits (Lachenmeier *et al*., 2006).

The procedures that combine sample extraction and subsequent GC–MS or GC–MS–MS are regarded as references for the analysis of ethyl carbamate in alcoholic beverages (Lachenmeier, 2005). Increasing requirements and cost pressures have forced both government and commercial food-testing laboratories to replace traditional reference methods with faster and more economical systems. Fourier-transform infrared spectroscopy, in combination with multivariate data analysis, has shown great potential for expeditious and reliable screening analysis of alcoholic beverages. The analysis of ethyl carbamate found in wine samples using Fourier-transform near-infrared spectroscopy was evaluated by Manley *et al*. (2001). Fourier-transform infrared spectroscopy in combination with partial least squares regression was applied to the screening analysis of ethyl carbamate in stone-fruit spirits (Lachenmeier, 2005).

1.2 Production and use

Ethyl carbamate can be made by the reaction of ethanol and urea or by warming urea nitrate with ethanol and sodium nitrite (Budavari, 2000). Another possible method is via addition of ethanol to trichloroacetyl isocyanate (Kocovský, 1986).

Production of ethyl carbamate was predominantly reported in the first half of the twentieth century. Ethyl carbamate has been produced commercially in the USA for at least 30 years (Tariff Commission, 1945). A major use of methyl and ethyl carbamate has been for the manufacture of meprobamate (Adams & Baron, 1965), and the spectacular success of this drug as a tranquilizer in the 1950s resulted in a demand for the commercial production of these intermediates. Ethyl carbamate had been used as a crease-resistant finish in the textile industry, as a solvent, in hair conditioners, in the preparation of sulfamic acids, as an extractant of hydrocarbons from crude oil and as a food flavour-enhancing agent (Adams & Baron, 1965). No data on the present use of ethyl carbamate in industry were available to the Working Group.

Ethyl carbamate was used in medical practice as a hypnotic agent at the end of nineteenth century but this use was discontinued after barbiturates became available. It was also tested for the treatment of cancers (Paterson *et al*., 1946; Hirschboeck *et al*., 1948), or used as a co-solvent in water for dissolving water-insoluble analgesics used for post-operative pain (Nomura, 1975). Ethyl carbamate has also been used in human medicine as an antileukaemic agent at doses of up to 3 g per day for the treatment of multiple myeloma (Adams & Baron, 1965). No evidence was available to the Working Group that ethyl carbamate is currently used in human medicine.

Ethyl carbamate is widely used in veterinary medicine as an anaesthetic for laboratory animals (Hara & Harris, 2002).

1.3 Occurrence and exposure

The occurrence of and exposure to ethyl carbamate in food have been reviewed (Battaglia *et al*., 1990; Zimmerli & Schlatter, 1991).

Ethyl carbamate has been detected in many types of fermented foods and beverages. The levels in wine and beer are in the microgram per litre range (Tables 1.2 and 1.3). Higher levels have been found in spirits, especially stone-fruit spirits, up to the milligram per litre range (Table 1.4). Ethyl carbamate has also been found in bread (Table 1.5). It may occur in fruit and vegetable juices at very low concentrations (< 1 µg/L) (Table 1.6). Its occurrence in other fermented food products (most notably fermented Asian products, such as soy sauce) is shown in Table 1.7.

In the past 20 years, major research has been carried out to identify the precursors of ethyl carbamate (Table 1.8) and develop methods for its reduction. One of the most established sources of ethyl carbamate is urea, which may be formed during the degradation of arginine by yeast. Arginase hydrolyses l-arginine to l-ornithine and urea (Schehl *et al*., 2007), and urea is secreted by the yeast into the medium where it reacts with ethanol to form ethyl carbamate (Ough *et al*., 1988a; Kitamoto *et al*., 1991; An & Ough, 1993). The addition of urease has been shown to reduce the content of ethyl carbamate in wine and other fermented products (Kobashi *et al*., 1988; Ough & Trioli, 1988; Tegmo-Larsson & Henick-Kling, 1990; Kim *et al*., 1995; Kodama & Yotsuzuka, 1996).

Ethyl carbamate may also be formed from cyanide. This may explain its high concentrations in stone-fruit spirits. The removal of cyanogenic glycosides such as amygdalin in stone-fruit by enzymatic action (mainly β-glucosidase) leads to the formation of cyanide (Lachenmeier *et al*., 2005b). Cyanide is oxidized to cyanate, which reacts with ethanol to form ethyl carbamate (Wucherpfennig *et al*., 1987; Battaglia *et al*., 1990; MacKenzie *et al*., 1990; Taki *et al*., 1992; Aresta *et al*., 2001). The wide range of concentrations of ethyl carbamate in stone-fruit spirits reflects its light- and time-dependent formation after distillation and storage (Andrey, 1987; Mildau *et al*., 1987; Baumann & Zimmerli, 1988; Zimmerli & Schlatter, 1991; Suzuki *et al*., 2001).

1.4 Regulations, guidelines and preventive actions

Public health concern regarding ethyl carbamate in food, and especially in alcoholic beverages, began in 1985 when relatively high levels were detected by Canadian authorities in alcoholic beverages, mainly in spirit drinks imported from Germany (Conacher & Page, 1986). Subsequently, Canada established an ethyl carbamate guideline of 30 µg/L for table wines, 100 µg/L for fortified wines, 150 µg/L for distilled spirits and 400 µg/L for fruit spirits (Conacher & Page, 1986). The Canadian guidelines were adopted by many other countries. The *Codex alimentarius* gives no specific standards for ethyl carbamate in food.

Table 1.2 Occurrence of ethyl carbamate in wine and fortified wine

Product	Year	No. of samples	Ethyl carbamate (μg/L)		Reference
			Mean	Range	
Wine	1951–89	127	0–5	0–48.6	Sponholz *et al*. (1991)
Wine	1988				Clegg *et al*. (1988)
White wines		196		<10–>100	
Red wines		51		<10–100	
Sparkling wines		14		–	
Wine coolers		2		–	
Fortified wines					
Sherries		256		<10–>200	
Ports		57		<10–>200	
Vermouths		7		<10–200	
Sherry	1985–87	12	32–33	<5–60	Dennis *et al*. (1989)
Wine		31	6	1–18	
Wine	1993				Sen *et al*. (1993)
White wines		16		ND–24	
Red wines		7		1–14	
Sake		2		3–29	
Sherry		6		28–69	
Fortified wines	1988–90	14	30	7–61	Vahl (1993)
Wine		57	7	<3–29	
Italian wine	2000	90			Cerutti *et al*. (2000)
Red				6–22	
White				6–16	
Rosé				7–15	
Brazilian wine	2002				Francisquetti *et al*. (2002)
Cabernet Sauvignon		30	10.6	2–31.8	
Merlot		17	6.6	1.8–32.4	
Gamay		3	4.5	3.4–6.5	
Pinot blanc		5	7.4	2.7–10.1	
Generic reds		9	16.6	2.4–36.2	
Gewürztraminer		12	10.1	1.2–30.5	
Italian Riesling		10	13.0	1.0–39.1	
Chardonnay		5	19.3	1.7–70	
Semillon		3	14.5	3.5–20.5	
Generic whites		3	4.8	4.7–5.1	
Common reds		10	5.1	2.1–9	
Sparkling wines		17	7.6	2.1–24.6	
Spanish red wine	2004	36		0–25	Uthurry *et al*. (2004)
Wine	2006	3	4.9	1.7–11.7	Ha *et al*. (2006)

ND, not detected

Table 1.3 Occurrence of ethyl carbamate in beer

Product	Year	No. of samples	Ethyl carbamate (µg/L)		Reference
			Mean	Range	
Beer	1985–87	15	0.1–1.1	<1–1.8	Dennis *et al*. (1989)
Beer	1989				Canas *et al*. (1989)
Domestic		33	0.24	ND–0.8	
Imported		36	2.8	2.1–3.5	
Danish Beer	1988–90	50	3	<0.2–6.6	Vahl (1993)
Alcohol-free beer	1994	4	0.3	0.1–0.7	Groux *et al*. (1994)
Beer		5	2.7	0.9–4.7	Groux *et al*. (1994)
Beer	1997				Dennis *et al*. (1997)
Draught		20		<1	
Canned		26		0.4–2.5	
Bottled		51		<1–14.7	
Home-brewed beer		32		<1–9	
Beer	2006	6	0.5	0.5–0.8	Ha *et al*. (2006)

ND, not detected

However, the general standard for contaminants and toxins in foods demands that contaminant levels shall be as low as reasonably achievable and that contamination may be reduced by applying appropriate technology in food production, handling, storage, processing and packaging (FAO/WHO, 2008).

Many preventive actions to avoid ethyl carbamate formation in food and beverages have been proposed (Table 1.9). For beverages such as wine and sake, the preventive measures have concentrated on yeast metabolism, whereas for stone-fruit spirits, research has been centred on reducing the precursor, cyanide. In addition, measures of good manufacturing practice such as the use of high-quality, unspoiled raw materials and high standards of hygiene during fermentation and storage of the fruit mashes, mashing and distillation must be optimized. To avoid the release of cyanide, it is essential to avoid breaking the stones, to minimize exposure to light and to shorten storage time. Some authors have proposed the addition of enzymes to decompose cyanide or a complete de-stoning of the fruit before mashing. The mashes have to be distilled slowly with an early switch to the tailing-fraction. Further preventive actions are the addition of patented copper salts to precipitate cyanide in the mash, distillation using copper catalysts or the application of steam washers (Zimmerli & Schlatter, 1991).

Table 1.4 Occurrence of ethyl carbamate in spirits

Product	Year	No. of samples	Ethyl carbamate (µg/L)		Reference
			Mean	Range	
Canadian whiskey	1988	18		<50–150	Clegg *et al*. (1988)
Rum		20		<50–150	
Vodka		5		<50	
Gin		4		<50	
Scotch whisky		7		<50–150	
Bourbon whiskey		19		<50–>150	
Fruit spirits and liqueurs		123		<50–>400	
Scotch whisky	1985–87	11	44	19–90	Dennis *et al*. (1989)
Imported whiskey		7	69–70	<5–206	
Vodka		3	ND	ND[a]	
Gin		3	ND	ND[a]	
Fruit spirit		4	41–42	<5–139	
Port		4	18	14–21	
Liqueur		8	129	9–439	
Whisky	1993	6	75.7	26–247	Sen *et al*. (1993)
Rye		1		8	
Bourbon		4		44–208	
Vodka		1		ND	
Gin		1		0.5	
Rum		1		19	
Fruit spirit		3		104–2344	
Apricot spirit		1		11	
Armagnac		2		410–432	
Other brandies		3		25–28	
Spirits	1988–90	22	534	<5–5103	Vahl (1993)
Grappa	2000	6		75–190	Cerutti *et al*. (2000)
Fruit spirit	2006	7	196.7	3.5–689.9	Ha *et al*. (2006)
Whisky		5	20.1	13.9–30.0	
Cheongju		5	20.2	8.4–30.3	
Korean style spirits	2000	10	3.4	ND–15.4	Kim *et al*. (2000)
Stone–fruit spirits	1986–2004	631	1400	10–18 000	Lachenmeier *et al*. (2005b)

ND, not detected; [a] Detection limit at 5 µg/L

Table 1.5 Occurence of ethyl carbamate in bread

Product	Year	No. of samples	Ethyl carbamate (µg/kg)		Reference
			Mean	Range	
Bread	1988	9	ND	ND[a]	Dennis *et al*. (1989)
Bread	1989	30			Canas *et al*. (1989)
White			3.0	ND–8	
Wheat			1.2	ND–4	
Other			0.9	ND–4	
Bread	1993	12	3.1	1.6–4.8	Sen *et al*. (1993)
Light toast	1993	12	4.3	1.3–10.9	
Dark toast	1993	12	15.7	4.9–29.2	
Bread	1988–90	33	3.5	0.8–12	Vahl (1993)
Bread	1994	48	5.2	0.5–27	Groux *et al*. (1994)

ND, not detected; [a] Detection limit at 5 µg/kg

Table 1.6 Occurrence of ethyl carbamate in juices

Product	Year	No. of samples	Ethyl carbamate (µg/L)		Reference
			Mean	Range	
Freshly pressed grape juices	1990	15		19–54	Tegmo-Larsson & Henick-Kling (1990)
Apple and pear juice	1994	6	ND	ND[a]	Groux *et al*. (1994)
Citrus juice		7	0.1	0–0.1	
Grape juice		6	0.1	0–0.2	
Other fruit juices		8	0.1	0–0.2	
Vegetable juice		3	0.1	0–0.1	

ND, not detected; [a] Detection limit at 0.06 ppb = 0.06 µg/L

Table 1.7 Occurrence of ethyl carbamate in miscellaneous fermented foods

Product	Year	No. of samples	Ethyl carbamate (µg/kg)		References
			Mean	Range	
Cheese	1989	16	ND	ND	Canas *et al*. (1989)
Yoghurt		12	0.4	ND–4	
Tea		6	ND	ND	
Yoghurt	1988	9	0–1	<1–<1	
Cheese		19	0.6–5.1	<5–6	
Soya sauce	1993	10		ND–59	Sen *et al*. (1993)
Yoghurt and buttermilk		14		ND–0.4	
Yoghurt and other acidified milk products	1988–90	19	0.2	<0.1–0.3	Vahl (1993)
Kimchi	2000	20	3.5	ND–16.2	Kim *et al*. (2000)
Soy sauce					
Regular		5	14.6	ND–19.5	
Traditional type		15	17.1	ND–73.3	
Soybean paste		7	2.3	ND–7.9	
Vinegar		5	1.2	0.3–2.5	
Soju	2006	7	3.0	0.8–10.1	Ha *et al*. (2006)
Takju		7	0.6	0.4–0.9	

ND, not detected

Table 1.8 Precursors of ethyl carbamate in different food matrices and factors that influence its formation

Precursor	Food matrix	Reference
Diethyl dicarbonate (used as food additive)	Orange juice, white wine, beer	Löfroth & Gejvall (1971)
Carbamyl phosphate (produced by yeasts)	Wine, fermented foods, bread	Ough (1976a)
Diethyl dicarbonate (used as food additive)	Wine	Ough (1976b)
Cyanide, vicinal dicarbonyl compounds	Model systems	Baumann & Zimmerli (1986b)
Carbamyl phosphate and ethyl alcohol, light	Wine	Christoph *et al*. (1987)
Cyanide, benzaldehyde, light	Distilled products	Christoph *et al*. (1988)
Light	Distilled products	Baumann & Zimmerli (1988)
Urea	Wine	Ough & Trioli (1988)
Urea, citrulline, *N*-carbamyl α-amino acids, *N*-carbamyl β-amino acid, allantoin, carbamyl phosphate	White and red wines	Ough *et al*. (1988a)
Amino acids, urea, ammonia	Chardonnay juice fermentation	Ough *et al*. (1988b)
Urea, copper, carbamyl phosphate, citrulline	Wine	Sponholz *et al*. (1991)
Cyanate, cyanide, cyanohydrin, copper cyanide complexes	Grain whisky	Aylott *et al*. (1990)
Cyanide related species (cyanide, copper cyanide complex, lactonitrile, cyanate, thiocyanate)	Scotch grain whisky	MacKenzie *et al*. (1990)
Cyanide	Grain-based spirits	Cook *et al*. (1990)
Cyanide	Grain-based spirits	McGill & Morley (1990)
Temperature, light	Wine	Tegmo-Larsson & Spittler (1990)
Cyanate	Alcoholic beverages	Taki *et al*. (1992)
Yeast strain, arginine, urea	Fortified wine	Daudt *et al*. (1992)
Isocyanate	Wine distillates	Boulton (1992)
Cyanide, copper, light,	Stone-fruit distillates	Kaufmann *et al*. (1993)
Manufacturing conditions	Soya bean tempe	Nout *et al*. (1993)
Urea	Wine	An & Ough (1993)

Table 1.8 (continued)

Precursor	Food matrix	Reference
Urea, citrulline	Wine	Stevens & Ough (1993)
Urea	Wine	Kodama *et al*. (1994)
Citrulline, arginine degradation	Wine	Liu *et al*. (1994)
Yeast arginase activity	Port	Watkins *et al*. (1996)
Azodicarbonamide (used as food additive)	Bread, beer	Dennis *et al*. (1997)
Citrulline	Wine	Mira de Orduña *et al*. (2000)
Citrulline	Model fortified wines	Azevedo *et al*. (2002)
Arginine	Wine	Arena *et al*. (2002)
Arginine	Korean soy sauce	Koh *et al*. (2003)
Storage time, temperature	Wine	Hasnip *et al*. (2004)
Arginine, citrulline	Wine	Arena & Manca de Nadra (2005)
Cyanide	Stone-fruit spirits	Lachenmeier *et al*. (2005b)
Fruit types, fermentation conditions	Fruit mashes	Balcerek & Szopa (2006)
Selected yeasts, different conditions (temperature, pH)	Red wine	Uthurry *et al*. (2006)
Yeast strain, arginine	Stone-fruit distillates	Schehl *et al*. (2007)

Table 1.9 Procedures for reducing ethyl carbamate concentration in different food matrices

Procedure	Food matrix	Reference
Modification of vineyard procedures Use of commercial yeast strains Urease treatment	Wine	Butzke & Bisson (1997)
Use of non-arginine-degrading oenococci	Wine	Mira de Orduña *et al*. (2001)
Metabolic engineering of *Saccharomyces cerevisiae*	Wine	Coulon *et al*. (2006)
Malolactic fermentation with pure cultures at low pH values (<3.5)	Wine	Terrade & Mira de Orduña (2006)
Removal of urea with an acid urease	Sake	Kobashi *et al*. (1988)
Genetic engineering of yeast	Sake	Kitamoto *et al*. (1991)
Non-urea producing yeast	Sake	Kitamoto *et al*. (1993)
Non-urea producing yeast	Sake	Yoshiuchi *et al*. (2000)
Application of acid urease	Takju	Kim *et al*. (1995)
Application of acid urease	Sherry	Kodama & Yotsuzuka (1996)
Precipitation of cyanide (steam washer)	Stone-fruit distillates	Nusser *et al*. (2001)
Application of cyanide catalyst Optimization of distillation conditions	Stone-fruit distillates	Pieper *et al*. (1992a,b)
Dark storage Separation of cyanide	Stone-fruit distillates	Christoph & Bauer-Christoph (1998, 1999)
Complete prevention of ethyl carbamate by state-of-the-art production technology	Stone-fruit distillates	Lachenmeier *et al*. (2005b)
De-stoning of the fruits	Stone-fruit distillates	Schehl *et al*. (2005)
Automatic rinsing of the stills, copper catalysts, separation of tailings, no re-distillation of tailings	Stone-fruit distillates	Weltring *et al*. (2006)
Yeast with reduced arginase activity	Stone-fruit distillates	Schehl *et al*. (2007)

Research on ethyl carbamate in food has led to a significant reduction in its content during the past 20 years. The use of additives that might be precursors of ethyl carbamate has been forbidden in most countries. For stone-fruit spirits — the most problematic food group — the few large distilleries that produce for the mass market have all introduced the good manufacturing practices described above and produce stone-fruit distillates that have only traces of ethyl carbamate. The current problem of ethyl carbamate encompasses in particular small distilleries that have not introduced improved technologies (Lachenmeier *et al*., 2005b).

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